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(54) **Title:** ARYL SUBSTITUTED IMIDAZONAPHTHYRIDINES

(57) **Abstract:** Imidazonaphthyridine ring systems substituted with an aryl substituent, pharmaceutical compositions containing the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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ARYL SUBSTITUTED IMIDAZONAPHTHYRIDINES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/581317, filed on June 18, 2004, which is incorporated herein by reference in its entirety.

BACKGROUND

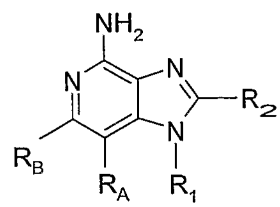
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-c]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in the imidazoquinoline ring system, as well as other imidazo ring systems, and there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



I

wherein R_A, R_B, R_1, and R_2, are as defined below.

The compounds of Formula I include various isomers of aryl substituted imidazonaphthyridines, in particular 1,5-naphthyridines, which are preferably substituted at the 7 position.

The compounds of Formula I are useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induce the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals (e.g., by inhibiting the induction of TNF-alpha). This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I, and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

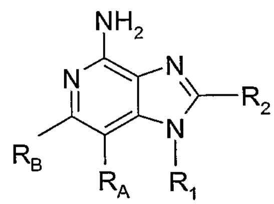
The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each

disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

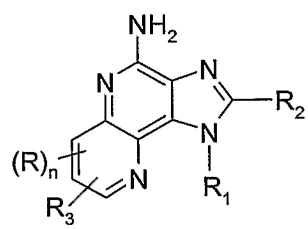
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula (I):

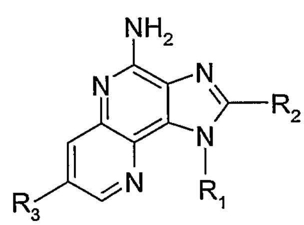


I

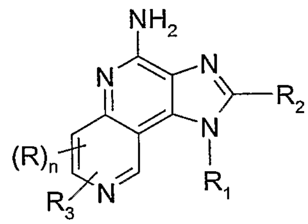
as well as more specific compounds of the following Formulas (II, III, IV, V, VI, and VII):



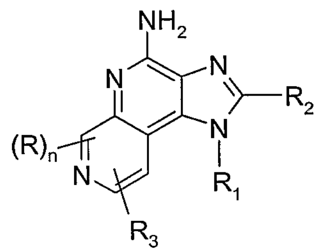
II



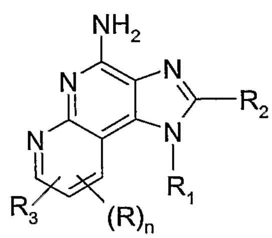
III



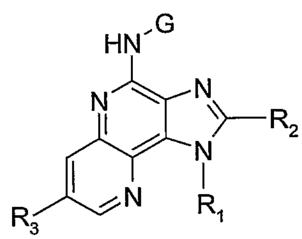
IV



V



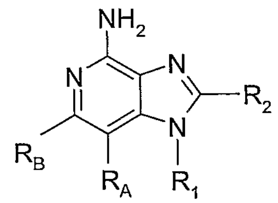
VI



VII

wherein R_A, R_B, R, R_1, R_2, R_3, G, and n are as defined below, and pharmaceutically acceptable salts thereof.

In one embodiment, there is provided a compound of the Formula (I):



I

wherein:

R_A and R_B join to form a fused pyridine ring which is substituted by one R_3 group or substituted by one R_3 group and one R group;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,

aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, alkoxyalkylenyl, α-aminocarboxyalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

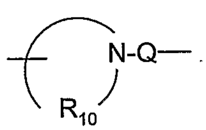
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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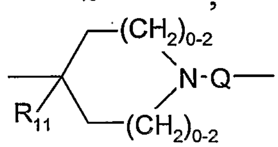

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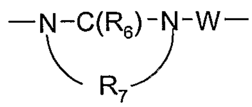
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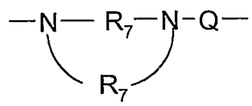
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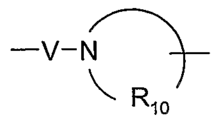
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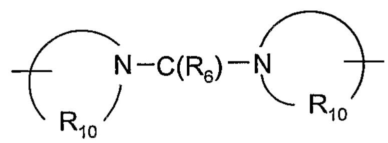
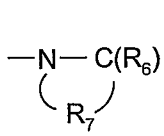
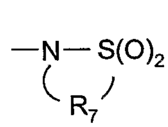
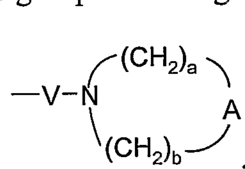
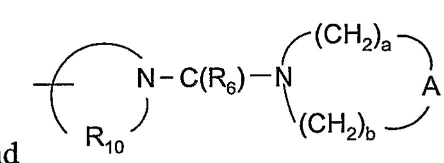

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, carboxy, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of fluoro, hydroxy, and alkoxy;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, -CH$_2$-, and -N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6), -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

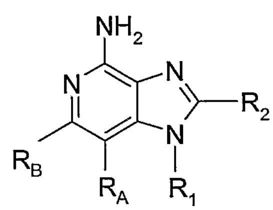
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, there is provided a compound of the Formula (I):



I

wherein:

R_A and R_B join to form a fused pyridine ring which is substituted by one R_3 group or substituted by one R_3 group and one R group;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

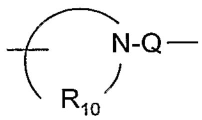
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,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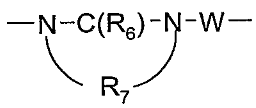
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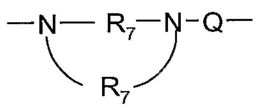
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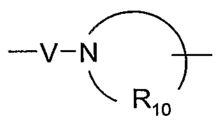
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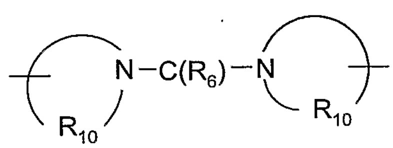
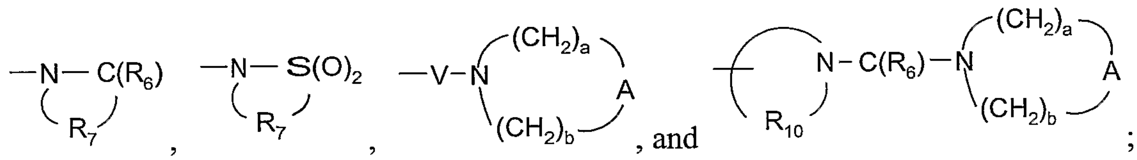

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} akylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, -CH$_2$-, and -N(R$_4$)-;

Q is selected from the group consisting of a bond, -C(R$_6$)-, -C(R$_6$)-C(R$_6$), -S(O)$_2$-, -C(R$_6$)-N(R$_8$)-W-, -S(O)$_2$-N(R$_8$)-, -C(R$_6$)-O-, and -C(R$_6$)-N(OR$_9$)-;

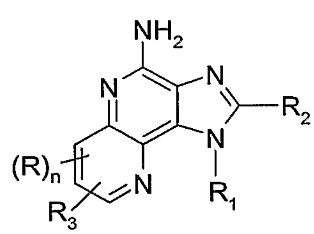
V is selected from the group consisting of -C(R$_6$)-, -O-C(R$_6$)-, -N(R$_8$)-C(R$_6$)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (II):



II

wherein:

n is 0 or 1;

R_1 is selected from the group consisting of:

-R$_4$,

-X-R$_4$,

-X-Y-R$_4$,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

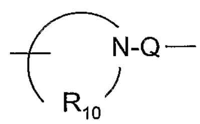
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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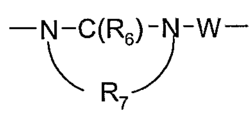
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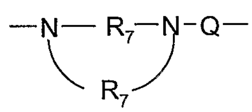
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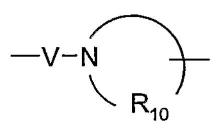
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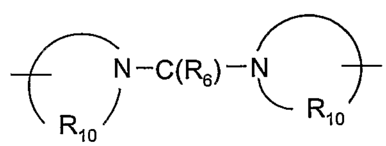
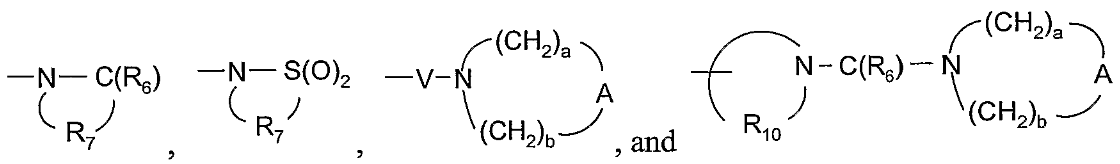

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,

nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

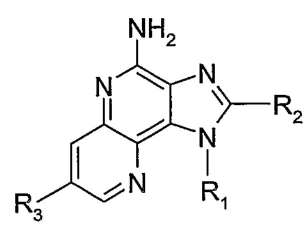
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (III):



III

wherein:

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

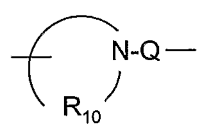
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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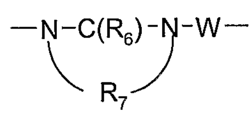

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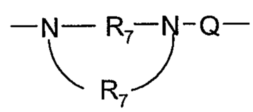

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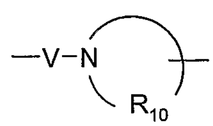

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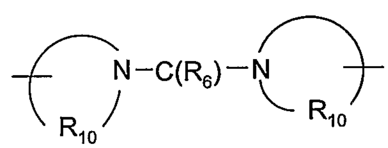


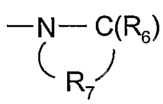
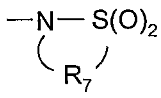
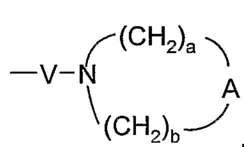
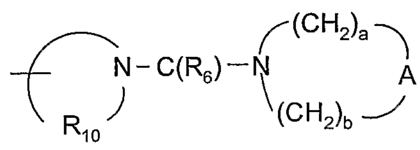
;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

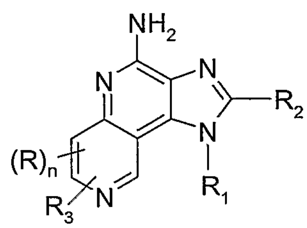
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula (IV):



IV

wherein:

n is 0 or 1;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,

haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

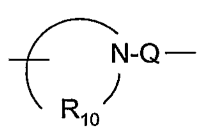
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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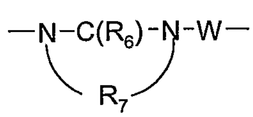

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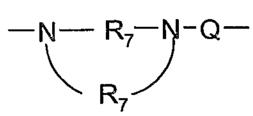

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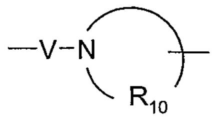
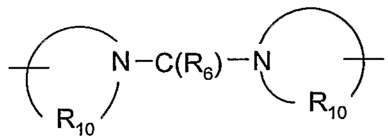
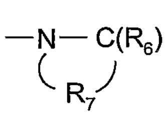
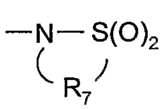
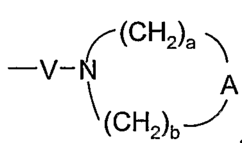
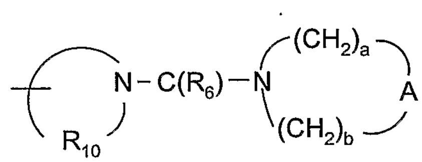
, and

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$,

-C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

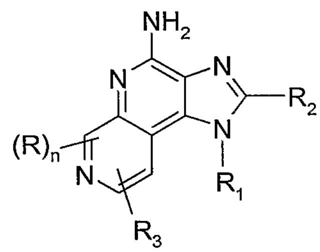
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (V):



V

wherein:

n is 0 or 1;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

$-Z-Ar'-X-R_5$;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

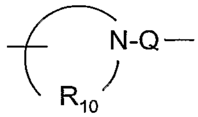
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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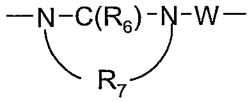
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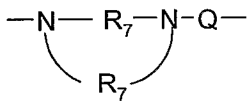
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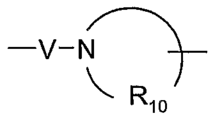
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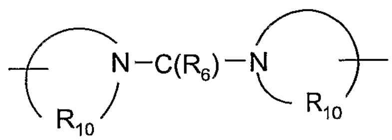
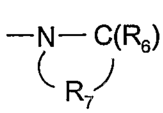
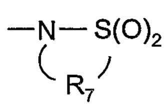
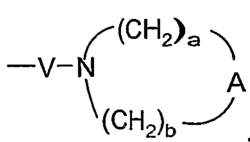
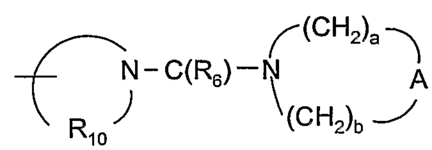

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, -CH$_2$-, and -N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6), -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

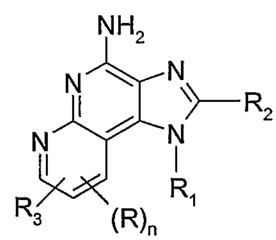
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (VI):



VI

wherein:

n is 0 or 1;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

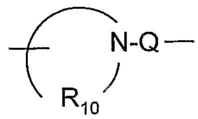
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,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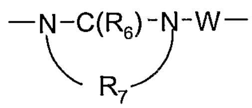
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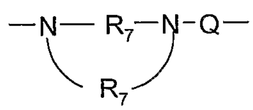
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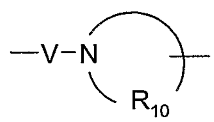
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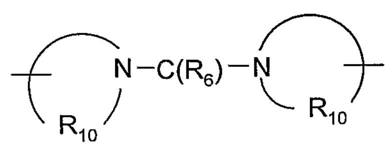
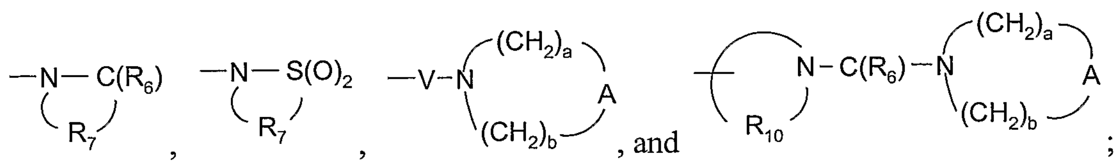

;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

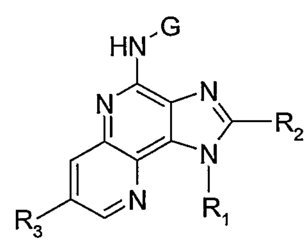
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a compound (which is a prodrug) of the Formula (VII):



VII

wherein:

G is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC$_{1-4}$ alkyl)Y$_0$,

-CH$_2$Y$_1$, and

-CH(CH$_3$)Y$_1$;

R' and R" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, arylC$_{1-4}$ alkylenyl, heteroarylC$_{1-4}$ alkylenyl, haloC$_{1-4}$ alkylenyl, haloC$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R" can also be hydrogen;

α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl;

Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxyC$_{1-6}$ alkylenyl, aminoC$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylaminoC$_{1-4}$ alkylenyl, and di-*N,N*-C$_{1-6}$ alkylaminoC$_{1-4}$ alkylenyl;

Y$_1$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N,N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl;

R$_1$ is selected from the group consisting of:

-R$_4$,

-X-R$_4$,

-X-Y-R$_4$,

-X-Y-X-Y-R$_4$, and

-X-R$_5$;

R$_2$ is selected from the group consisting of:

-R$_4$,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4,

-Z-Ar'-X-Y-R_4,

-Z-Ar'-R_5, and

-Z-Ar'-X-R_5;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

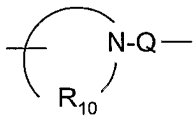
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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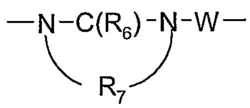

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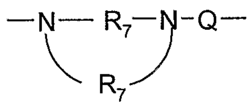

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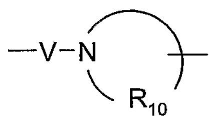

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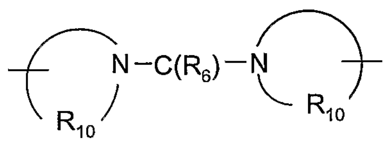
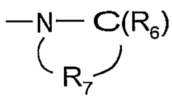
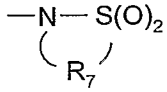
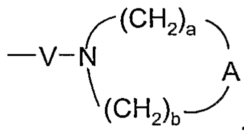
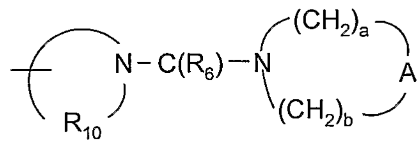


;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

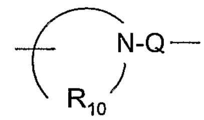
For any of the compounds presented herein, each one of the following variables (e.g., Z, X, Y, R_A, R_B, R_1, R_2, R_3, Q, n, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments of Formulas II, IV, V, and VI, n is 0 or 1. For certain embodiments of Formulas II, IV, V, and VI, n is 0.

For certain embodiments, R is selected from the group consisting of alkyl, alkoxy, chloro, fluoro, hydroxy, and trifluoromethyl.

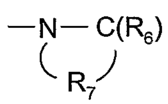
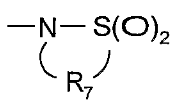
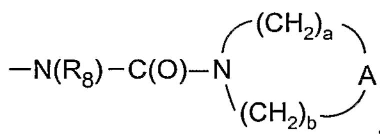
For certain embodiments, R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X-Y-R_4$, and $-X-R_5$.

For certain embodiments, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, fluoroalkyl, heterocyclylalkylenyl which is unsubstituted or substituted by hydroxy, -X-Y-R_4, and -X-R_5. For certain alternative embodiments, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalky, -X-Y-R_4, and -X-R_5. Preferably, X is alkylene. Preferably, Y is selected from the group consisting of

-N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -S(O)$_2$-, and  .

Preferably, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

Preferably, R_5 is selected from the group consisting of

 ,  , and  .

For certain embodiments, R_1 is selected from the group consisting of alkyl and hydroxyalkyl.

For certain embodiments, R_1 is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-[(methylsulfonyl)amino]butyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, (1-hydroxycyclopentyl)methyl, (1-hydroxycyclobutyl)methyl, 2-fluoro-2-methylpropyl, tetrahydro-2*H*-pyran-4-ylmethyl, and 4-hydroxytetrahydro-2*H*-pyran-4-ylmethyl.

For certain embodiments, R_1 is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 4-[(methylsulfonyl)amino]butyl, and 2-fluoro-2-methylpropyl.

For certain embodiments, R_1 is selected from the group consisting of 2-hydroxy-2-methylpropyl, 2-methylpropyl, propyl, 2,3-dihydroxypropyl, 2-methyl-2-[(methylsulfonyl)amino]propyl (i.e., 2-methanesulfonylamino-2-methylpropyl), and 4-[(methylsulfonyl)amino]butyl (i.e., 4-methanesulfonylaminobutyl).

For certain embodiments, R_2 is selected from the group consisting of -R_4, -X-R_4, -X-Y-R_4, and -X-R_5.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl. For certain embodiments, R_2 is selected from the group consisting of methyl, ethyl, propyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, R_2 is selected from the group consisting of methyl, ethyl, propyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

For certain embodiments, R_3 is selected from the group consisting of -Z-Ar, -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, -Z-Ar'-R_5, and -Z-Ar'-X-R_5.

For certain embodiments, R_3 is -Z-Ar.

For certain embodiments, R_3 is selected from the group consisting of phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, pyrimidinyl, furyl, and quinolinyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, alkenyl, hydroxy, hydroxyalkyl, alkoxy, amino, aminoalkyl, cyano, methylenedioxy, arylalkyleneoxy, carboxy, haloalkyl, and dialkylamino.

For certain other embodiments, R_3 is selected from the group consisting of phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, pyrimidinyl, and furyl; each of which can be unsubstituted or can be substituted by one or more substituents selected from the group consisting of halogen, alkyl, alkenyl, hydroxy, hydroxyalkyl, alkoxy, amino, aminoalkyl, and cyano.

For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, 3-(morpholin-4-ylcarbonyl)phenyl, 3-[(isopropylamino)carbonyl]phenyl,

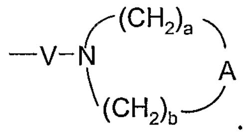
3-[(propylamino)carbonyl]phenyl, phenyl, 3-(hydroxymethyl)phenyl, 6-fluoropyridin-3-yl, 4-chlorophenyl, 2-hydroxyphenyl, 2-isopropoxyphenyl, 3,4-difluorophenyl, 3-[(methylsulfonyl)amino]phenyl, 4-[(methylsulfonyl)amino]phenyl, and 3-(aminocarbonyl)phenyl.

For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl (i.e., 3-pyridyl), pyridin-4-yl (i.e., 4-pyridyl), 5-(hydroxymethyl)pyridin-3-yl (i.e., 5-hydroxymethyl-3-pyridyl), 2-ethoxyphenyl, and 3-(morpholin-4-ylcarbonyl)phenyl (i.e., 3-(morpholine-4-carbonyl)phenyl). For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl, 3-[(isopropylamino)carbonyl]phenyl, 3-[(propylamino)carbonyl]phenyl, 3-(morpholin-4-ylcarbonyl)phenyl, 3-[(methylsulfonyl)amino]phenyl, 5-(hydroxymethyl)pyridin-3-yl, and 6-fluoropyridin-3-yl.

For certain other embodimentds, R_3 is -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, -Z-Ar'-R_5, or -Z-Ar'-X-R_5. For certain embodiments, R_3 is -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, or -Z-Ar'-R_5.

Preferably, for certain embodiments, Ar' (of -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, -Z-Ar'-R_5, or -Z-Ar'-X-R_5 and more particularly of -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, or -Z-Ar'-R_5) is phenylene or pyridylene. Preferably, for certain embodiments, Y in -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4 is selected from the group consisting of: -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(O)-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -C(O)-O-, and -C(O)-N(OCH$_3$)-. Preferably, for certain embodiments, Y in -Z-Ar'-Y-R_4 or –Z-Ar'-X-Y-R_4 is selected from the group consisting of -S(O)$_{0-2}$-, -C(O)-, -N(R_8)-Q-, and –C(R_6)-N(R_8)-. Preferably, in such embodiments, Q is selected from the group consisting of bond, -C(O)-, -C(O)-O-, -C(O)-N(H)-, and -S(O)$_2$-. Moe preferably, in such embodiments, Q is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, and -S(O)$_2$–. Preferably, in such embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and alkoxyalkylenyl. Preferably, for certain embodiments, X in -Z-Ar'-X-Y-R_4 or -Z-Ar'-X-R_5 (more particularly in -Z-Ar'-X-Y-R_4) is C_{1-4} alkylene. Preferably, for certain embodiments, R_4 in -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, and heterocyclyl. Preferably, for certain other embodiments, R_4 in -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4 is selected from the group consisting of alkyl, haloalkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, alkylheteroarylenyl, and heterocyclyl, preferably, with the proviso that R_4 may also be

hydrogen when Y is -C(O)-O-, -C(O)-N(OCH_3)-, or -N(R_8)-. Preferably, for certain embodiments, R_5 in -Z-Ar'-R_5 or -Z-Ar'-X-R_5 (more particularly in -Z-Ar'-R_5) is



For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl (i.e., 3-pyridyl), 3-[(isopropylamino)carbonyl]phenyl, 3-[(propylamino)carbonyl]phenyl, and 3-(morpholin-4-ylcarbonyl)phenyl (i.e., 3-(morpholine-4-carbonyl)phenyl).

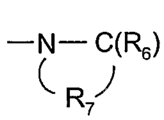
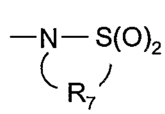
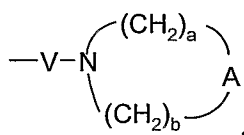
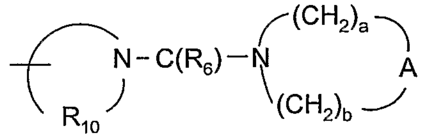
For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, carboxy, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

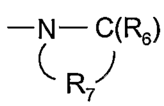
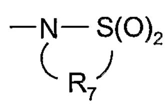
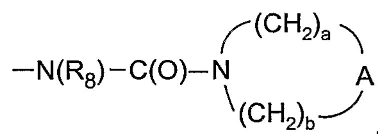
For certain embodiments, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl. For certain embodiments, particularly in -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4,

R_4 is selected from the group consisting of alkyl, haloalkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, alkylheteroarylenyl, and heterocyclyl, preferably with the proviso that R_4 may also be hydrogen when Y is -C(O)-O-, -C(O)-N(OCH_3)-, or -N(R_8)-. For certain embodiments, particularly in -Z-Ar'-Y-R_4 or -Z-Ar'-X-Y-R_4, R_4 is selected from the group consisting of alkyl, aryl, arylalkylenyl, heteroarylalkylenyl, heteroaryl, and heterocyclyl.

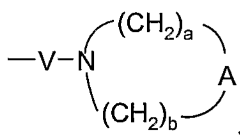
For certain embodiments, R_5 is selected from the group consisting of:

 ,  ,  , and  .

For certain embodiments, R_5 is selected from the group consisting of

 ,  , and  .

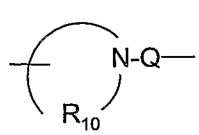
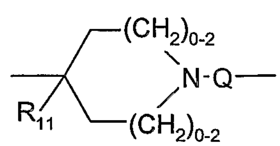
For certain embodiments, particularly in -Z-Ar'-R_5 or -Z-Ar'-X-R_5, R_5 is

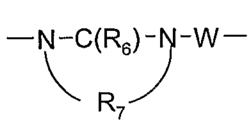
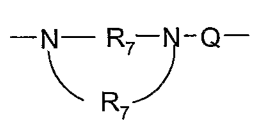
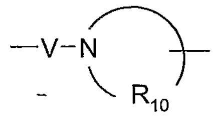
 .

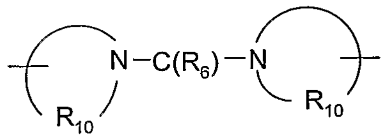
For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups.

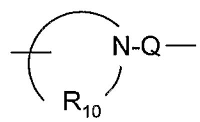
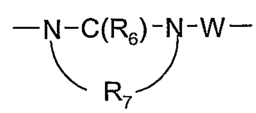
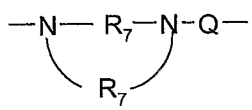
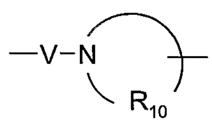
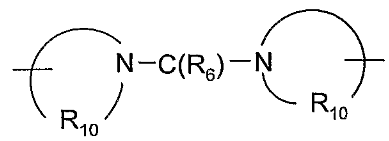
For certain embodiments, X is alkylene.

For certain embodiments, particularly in -Z-Ar'-X-Y-R_4 or -Z-Ar'-X-R_5, X is C_{1-4} alkylene.

For certain embodiments, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,  ,  ,

, , , and

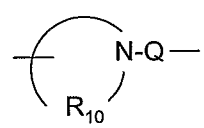
.

For certain embodiments, Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, , , , , and .

For certain embodiments, Y is selected from the group consisting of $S(O)_{0-2}-$, $-C(O)-$, $-N(R_8)-Q-$, and $-C(R_6)-N(R_8)-$.

For certain embodiments, particularly in $-Z-Ar'-Y-R_4$ or $-Z-Ar'-X-Y-R_4$, Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(O)-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-C(O)-O-$, and $-C(O)-N(OCH_3)-$.

For certain embodiments, particularly in $-Z-Ar'-Y-R_4$ or $-Z-Ar'-X-Y-R_4$, Y is selected from the group consisting of $-S(O)_{0-2}-$, $-C(O)-$, $-N(R_8)-Q-$, and $-C(R_6)-N(R_8)-$.

For certain embodiments, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, $-S(O)_2-$, and .

For certain embodiments, Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene. For certain embodiments, Z is selected from the group consisting of a bond, methylene, and ethylene. For certain embodiments, Z is a bond.

For certain embodiments, Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto,

cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, alkoxyalkylenyl, α-aminocarboxyalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino.

For certain embodiments, Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, aminoalkyl, alkylamino, and dialkylamino.

For certain embodiments of Formulas I, II, and III, Ar may also be aryl or heteroaryl substituted by alkoxyalkylenyl.

For certain embodiments, Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino.

For certain embodiments, particularly in -Z-Ar'-Y-R_4, -Z-Ar'-X-Y-R_4, or -Z-Ar'-R_5, Ar' is phenylene or pyridylene.

For certain embodiments, Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6), -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-. For certain embodiments, particularly embodiments of -N(R_8)-Q-, Q is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, -C(O)-N(H)-, and -S(O)$_2$-. For certain embodiments, particularly embodiments of -N(R_8)-Q-, Q is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, and -S(O)$_2$-. For certain embodiments, Q is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, and -S(O)$_2$-.

For certain embodiments, R_6 is =O or =S. For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene. For certain embodiments, R_7 is C_{2-3} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl. For certain embodiments, particularly in $-N(R_8)-Q-$ and $-C(R_6)-N(R_8)-$, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and alkoxyalkylenyl. For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_9 is hydrogen or alkyl. For certain embodiments, R_9 is hydrogen or methyl.

For certain embodiments, R_{10} is C_{3-8} alkylene. For certain embodiments, R_{10} is C_5 alkylene.

For certain embodiments, R_{11} is selected from the group consisting of fluoro, hydroxy, and alkoxy.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$. For certain embodiments, A is -O-, $-CH_2-$, or -C(O)-.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$. For certain embodiments, V is -C(O)-. For certain embodiments, V is $-N(R_8)-C(R_6)-$. For certain embodiments, V is $-S(O)_2-$.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and $–S(O)_2-$. For certain embodiments, W is a bond.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

For certain embodiments, a is 2.

For certain embodiments, b is 2.

For certain embodiments of the compounds of Formulas (I) through (VI), the $–NH_2$ group can be replaced by an -NH-G group, as shown in the compound of Formula (VII), to form prodrugs. In such embodiments, G is selected from the group consisting of: -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', $-CH(OC_{1-4}\text{ alkyl})Y_0$, $-CH_2Y_1$, and $-CH(CH_3)Y_1$. For certain embodiments, G is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, and -C(O)-O-R'. Preferably, R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl,

haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen. Preferably, α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl. Preferably, Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl. Preferably, Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

In one embodiment, there is provided a pharmaceutical composition containing an effective amount of a compound of Formula VII. In one embodiment, there is provided a method of inducing cytokine biosynthesis in an animal by administering an effective amount of a compound of Formula VII to the animal. In one embodiment, there is provided a method of treating a viral infection in an animal by administering an effective amount of a compound of Formula VII to the animal. In one embodiment, there is provided a method of treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula VII to the animal.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, up to 5 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. Likewise, "alkylenyl," "alkenylenyl," and "alkynylenyl" are the divalent forms of the "alkyl,"

"alkenyl," and "alkynyl" groups defined above. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and/or N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can

include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula -N(R_8)-C(O)-N(R_8)- each R_8 group is independently selected. In another example, when an R_2 and an R_3 group both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Y group is present (i.e., R_2 and R_3 both contain a Y group) and each Y group contains one or more R_7 groups, then each Y group is independently selected, and each R_7 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by vaious mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W.

Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-

fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention or pharmaceutically acceptable salts thereof, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

Compounds of the invention can be prepared according to Reaction Scheme I where R_{3a} is -Z_a-Ar, -Z_a-Ar'-Y-R_4, -Z_a-Ar'-X-Y-R_4, or- Z_a-Ar'-R_5; Z_a is a bond, alkenylene, or alkynylene; Hal is bromo or iodo; and R, n, Ar, Ar', X, Y, R_4, and R_5 are as defined above. R_{1a} and R_{2b} are subsets of R_1 and R_2 as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to oxidation in step (8). These substituents include -S- and heteroaryl groups.

In step (1) of Reaction Scheme I, an aminopyridine of Formula X is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XI. The reaction is conveniently carried out by adding a solution of an aminopyridine of Formula X to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature, such as 70 °C. Aminopyridines of Formula X are commercially available, or they can be prepared by known methods.

In step (2) of Reaction Scheme I, an imine of Formula XI undergoes thermolysis and cyclization to provide a [1,5]naphthyridin-4-ol of Formula XII. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature not lower than about 200 °C and not higher than about 250 °C.

In step (3) of Reaction Scheme I, the [1,5]naphthyridin-4-ol of Formula XII is nitrated under conventional nitration conditions to provide a 3-nitro[1,5]naphthyridin-4-ol of Formula XIII. The reaction is conveniently carried out by heating the

[1,5]naphthyridin-4-ol of Formula XII in nitric acid at an elevated temperature, such as 90 °C.

In step (4) of Reaction Scheme I, a 3-nitro[1,5]naphthyridin-4-ol of Formula XIII is chlorinated using conventional chlorination chemistry to provide a 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV. The reaction is conveniently carried out by treating the 3-nitro[1,5]naphthyridin-4-ol of Formula XIII with phosphorous oxychloride in a suitable solvent, such as *N,N*-dimethylformamide (DMF). The reaction can be carried out at ambient temperature or at an elevated temperature, such as 100 °C.

In step (5) of Reaction Scheme I, a 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV is treated with an amine of Formula R_{1a}-NH_2 to provide a 3-nitro[1,5]naphthyridin-4-amine of Formula XV. Several amines of Formula R_{1a}-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding the amine of Formula R_{1a}-NH_2 to a solution of the 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV in a suitable solvent, such as dichloromethane or methanol, in the presence of a tertiary amine, such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as, for example, 0 °C.

In step (6) of Reaction Scheme I, a 3-nitro[1,5]naphthyridin-4-amine of Formula XV is reduced to provide a [1,5]naphthyridine-3,4-diamine of Formula XVI. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent, such as toluene, methanol, or acetonitrile, or a suitable solvent mixture, such as acetonitrile:methanol or acetonitrile:isopropyl alcohol. The reaction can be carried out at ambient temperature.

Alternatively, the reduction in step (6) can be carried out using a one- or two-phase sodium dithionite reduction. The reaction is conveniently carried out using the conditions described by Park, K.K.; Oh, C.H.; and Joung, W. K.; *Tetrahedron Lett.*, *34*, pp. 7445-7446 (1993) by adding sodium dithionite to a compound of Formula XV in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and ethyl viologen dibromide, ethyl viologen diiodide, or 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide.

In step (7) of Reaction Scheme I, a [1,5]naphthyridine-3,4-diamine of Formula XVI is treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XVII. Suitable carboxylic acid equivalents include orthoesters of Formula $R_{2a}C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_{2a}C(O\text{-alkyl})_2(O\text{-}C(O)\text{-alkyl})$, and acid chlorides of Formula $R_{2a}C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_{2a}. For example, triethyl orthoformate will provide a compound where R_{2a} is hydrogen, and trimethyl orthovalerate will provide a compound where R_{2a} is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a [1,5]naphthyridine-3,4-diamine of Formula XVI in a suitable solvent, such as toluene or xylenes. Optionally, catalytic pyridine hydrochloride can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction. Conveniently, a Dean-Stark trap can be used to collect the volatiles.

Alternatively, step (7) can be carried out in two steps when an acid chloride of Formula $R_{2a}C(O)Cl$ is used as the carboxylic acid equivalent. Part (i) of step (7) is conveniently carried out by adding the acid chloride to a solution of a [1,5]naphthyridine-3,4-diamine of Formula XVI in a suitable solvent, such as dichloromethane, chloroform, or acetonitrile, or mixtures thereof, to afford an amide. Optionally, a tertiary amine, such as triethylamine, pyridine, or 4-dimethylaminopyridine, can be added. The reaction can be carried out at ambient temperature. The amide product can be isolated and optionally purified using conventional techniques. Part (ii) of step (7) can be carried out by heating, for example, at reflux, the amide prepared in part (i) to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XVII. The reaction is conveniently carried out in a suitable solvent, such as toluene, at a temperature sufficient to drive off water formed during the reaction. The reaction can also be carried out in a solvent, such as ethanol or methanol, in the presence of a base, such as triethylamine or aqueous potassium carbonate.

In step (8) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XVII is oxidized to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*–oxide of Formula XVIII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XVII in a solvent, such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature.

In step (9) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XVIII is aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX. Step (9) can be carried out by the activation of an *N*-oxide of Formula XVIII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides, such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts, such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XVIII in a suitable solvent, such as dichloromethane or chloroform, and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature.

Steps (8) and (9) can alternatively be combined and carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XVII in a solvent, such as dichloromethane or chloroform, and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide of Formula XVIII.

Step (10) of Reaction Scheme I can be carried out using known palladium-catalyzed coupling reactions, such as the Suzuki coupling, the Stille coupling, the Sonogashira coupling, and the Heck reaction. For example, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX undergoes Suzuki coupling with a boronic acid of Formula R_{3a}-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide an 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula IIa, a subgenus of Formulas I and II, wherein R_{3a} is as defined above and Z_a is a bond or alkenylene. The coupling is carried out by combining a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base, such as sodium carbonate or sodium bicarbonate, in a suitable solvent or solvent mixture, such as *n*-propanol:water. The coupling reaction may also conveniently carried out by heating a mixture of a compound of Formula XIX, a boronic acid or an ester or anhydride thereof, potassium carbonate and catalytic dichlorobis(triphenylphosphine)palladium(II) in a suitable solvent or solvent mixture, such as dimethoxyethane (DME) and water. Suzuki coupling reactions may be carried out under an inert atmosphere, such as nitrogen or

argon. The reactions can be carried out at an elevated temperature, for example, at the reflux temperature of the solvent, typically at a temperature not lower than 80 °C and not higher than 120 °C. Numerous boronic acids of Formula R_{3a}-B(OH)$_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, 5394-5397 (2002).

The Heck reaction can also be used in step (10) of Reaction Scheme I to provide compounds of Formula IIa, wherein R_{3a} is as defined above and -Z_a is alkenylene. The Heck reaction is carried out by coupling a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX with a compound of the Formula H_2C=C(H)-Ar_a, wherein Ar_a is -Ar, -Ar'-Y-R_4, -Ar'-X-Y-R_4, or -Ar'-R_5. Several of these vinyl-substituted compounds, for example, compounds of the Formulas H_2C=C(H)-Ar, H_2C=C(H)-Ar'-Y-R_4, and H_2C=C(H)-Ar'-X-Y-R_4 are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base, such as triethylamine, in a suitable solvent, such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature not lower than 80 °C and not higher than about 120 °C under an inert atmosphere.

Compounds of Formula IIa, wherein R_{3a} is defined as above Z_a is alkynylene, can also be prepared by palladium catalyzed coupling reactions, such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIX with a compound of the Formula H-C≡C-Ar, (alkyl)$_3$Sn-C≡C-Ar, or (alkyl)$_3$Si-C≡C-Ar, wherein Ar is as defined above.

Isomers of the compound of Formula X or Formula XII are also available or can be synthesized and can be used to prepare compounds of Formulas IV, V, and VI according to the methods shown in Reaction Scheme I.

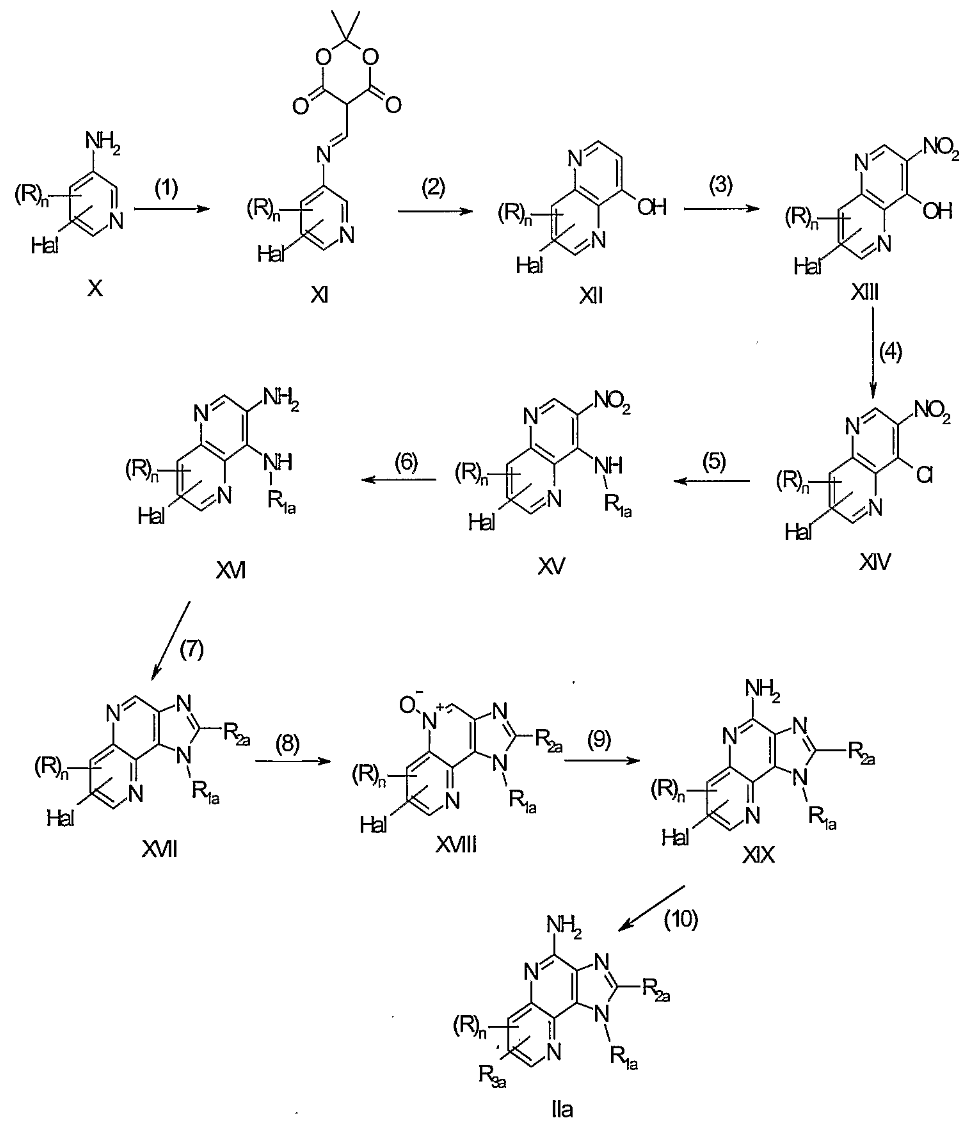
For some embodiments, compounds in Reaction Scheme I can be further elaborated using conventional synthetic methods. For example, an amine of Formula R_{1a}-NH_2 may be substituted by a hydroxy or second amino group, which may be further functionalized before step (7) of Reaction Scheme I or later in the synthetic route. Several examples of synthetic elaborations of an R_{1a} group on a 1*H*-imidazo[4,5-*c*]quinoline or a

1*H*-imidazo[4,5-*c*]naphthyridine are known and can be used to provide a compound of Formula II wherein R_1 is as defined above. See, for example, U.S. Patent Nos. 4,689,338 (Gerster), 4,929,624 (Gerster et al.), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,194,425 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.), 6,660,747 (Crooks et al.), 6,670,372 (Charles et al.), 6,683,088 (Crooks et al.), 6,656,938 (Crooks et al.), 6,664,264 (Dellaria et al.), 6,677,349 (Griesgraber), and 6,664,260 (Charles et al.), and U.S. Patent Publication Application No. US 2004/0147543 (Hays et al.).

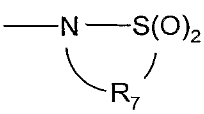
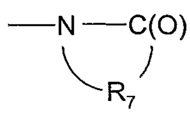
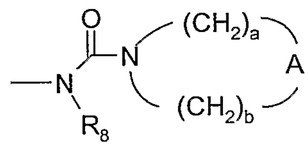
Similar synthetic transformations can be made at R_{2a} if, for example, the acid chloride used in step (7) of Reaction Scheme I contains a protected hydroxy or amino group, and these synthetic transformations can be used to provide compounds of Formula II, wherein R_2 is as defined above. Some acid chlorides of this type are commercially available; others can be prepared by known synthetic methods. A protected hydroxy or amino group thus installed at the R_{2a} position can then be deprotected by a variety of methods well known to one of skill in the art. For example, a hydroxyalkylenyl group is conveniently introduced at the R_{2a} position by the dealkylation of a methoxy- or ethoxyalkylenyl group, which can be installed by using a methoxy- or ethoxy-substituted carboxylic acid equivalent, for example, methoxyacetyl chloride, 2-methoxypropionyl chloride, or ethoxyacetyl chloride, in step (7) of Reaction Scheme I or step (3) in Reaction Scheme II below. The dealkylation can be carried out by treating a compound wherein R_{2a} is an alkoxyalkylenyl group with boron tribromide in a suitable solvent such as dichloromethane at a sub-ambient temperature such as 0 °C. Alternatively, acetoxyacetyl chloride can be used in step (7) of Reaction Scheme I, and hydrolysis of the ester group to reveal a hydroxy group can be carried out by conventional methods. The resulting hydroxy group may then be oxidized to an aldehyde or carboxylic acid or converted to a leaving group such as, for example, a chloro group using thionyl chloride or a trifluoromethanesulfonate group using trifluoromethanesulfonic anhydride. The resulting leaving group can then be displaced by a variety of nucleophiles. Sodium azide can be used as the nucleophile to install an azide group, which can then be reduced to an amino group using heterogeneous hydrogenation conditions. An amino group at the R_2 position can be converted to an amide, sulfonamide, sulfamide, or urea using conventional methods, such as those described in step (5) of Reaction Scheme II below. A leaving

group at R_2, such as a chloro or trifluoromethanesulfonate group, can also be displaced with a secondary amine, a substituted phenol, or a mercaptan in the presence of a base such as potassium carbonate. For examples of these and other methods used to install a variety of groups at the R_2 position, see U.S. Patent No. 5,389,640 (Gerster et al.). These synthetic transformations may conveniently be carried out as the last steps in the synthesis.

Reaction Scheme I



Compounds of the invention, where R_{1b} is -X-N(R_8)-Q-R_4 or -X-R_5, wherein R_5 is

, , or ; and A, X, Q, R, R_{2a}, R_{3a}, R_7, R_8, Hal, a, b, and n are as defined above, can be prepared according to Reaction Scheme II.

In step (1) of Reaction Scheme II, a 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV is treated with a Boc-protected diamine of Formula $(CH_3)_3CO\text{-}C(O)\text{-}NH\text{-}X\text{-}NH_2$ to provide a 3-nitro[1,5]naphthyridin-4-amine of Formula XX. Several Boc-protected diamines of Formula $(CH_3)_3CO\text{-}C(O)\text{-}NH\text{-}X\text{-}NH_2$ are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding a solution of the Boc-protected diamine of Formula $(CH_3)_3CO\text{-}C(O)\text{-}NH\text{-}X\text{-}NH_2$ to a cooled solution of the 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV in a suitable solvent, such as dichloromethane, in the presence of a tertiary amine, such as triethylamine. The reaction can be carried out at ambient temperature. Alternatively, a 4-chloro-3-nitro[1,5]naphthyridine of Formula XIV can be combined with a diamine of Formula $NH_2\text{-}X\text{-}NH_2$ under the conditions described above, and the product can be protected with a Boc group using conventional methods.

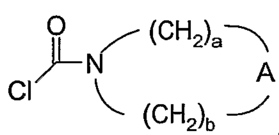
In steps (2) and (3) of Reaction Scheme II, a 3-nitro[1,5]naphthyridin-4-amine of Formula XX is first reduced to provide a [1,5]naphthyridine-3,4-diamine of Formula XXI, which is converted to 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXII by reaction with a carboxylic acid equivalent. Steps (2) and (3) of Reaction Scheme II can be carried out as described for steps (6) and (7) of Reaction Scheme I.

In step (4) of Reaction Scheme II, the Boc-protecting group of a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXII is removed to provide a 1-aminoalkyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII. The reaction is conveniently carried out by adding hydrochloric acid or a solution of hydrochloric acid in ethanol to a solution of a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXII in a suitable solvent, such as ethanol. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent, or at ambient temperature.

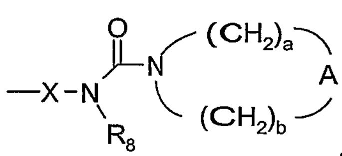
In step (5) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII is converted to a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV, where R_{1b} is as defined above, using conventional methods. For example, a 1*H*-

imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XXIV in which R_{1b} is $-X-N(R_8)-Q-R_4$, and Q is -C(O)-. In addition, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII can react with sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XXIV in which R_{1b} is $-X-N(R_8)-Q-R_4$, and Q is $-S(O)_2-$. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a solution of the 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII in a suitable solvents such as chloroform, dichloromethane, or DMF. Optionally a base, such as triethylamine or *N,N*-diisopropylethylamine, can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C.

Ureas of Formula XXIV can be prepared by reacting a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII with isocyanates of Formula $R_4N{=}C{=}O$ or Formula $R_4(CO)N{=}C{=}O$, isothiocyanates of Formula $R_4N{=}C{=}S$, sulfonyl isocyanates of Formula $R_4S(O)_2N{=}C{=}O$, or carbamoyl chlorides of Formula $R_4N-(R_8)-C(O)Cl$ or

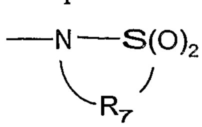


. Numerous compounds of these types are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out as described above for the reaction of a compound of Formula XXIII with acid chlorides or sulfonyl chlorides to provide a compound of Formula XXIV wherein R_{1b} is $-X-N(R_8)-Q-R_4$ or

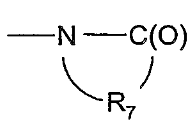


, in which Q is $-C(R_6)-N(R_8)-W-$, and R_6, R_8, W, A, a, and b are as defined above.

Compounds of Formula XXIV where R_{1b} is $-X-R_5$ and R_5 is



or



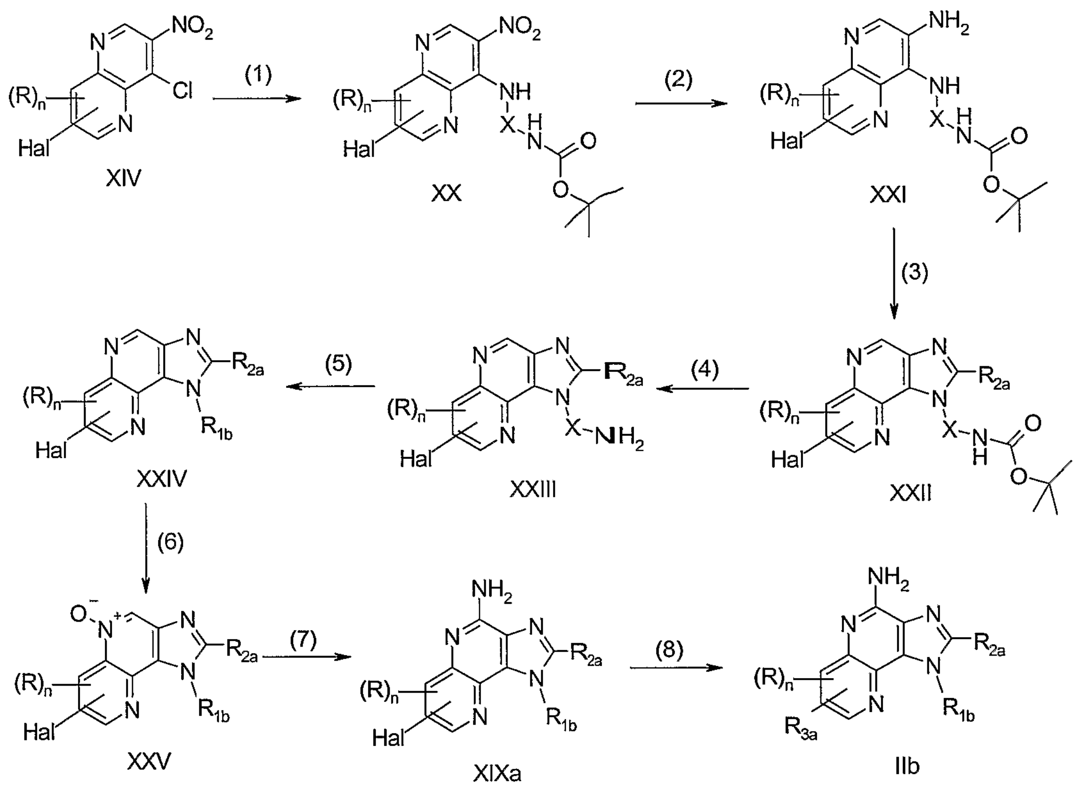
can be prepared by treating an amino-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII with a chloroalkanesulfonyl chloride of Formula Cl-$R_7S(O)_2Cl$ or a chloroalkanoyl chloride of Formula Cl-$R_7C(O)Cl$. The reaction is conveniently carried out by adding the chloroalkanesulfonyl chloride or chloroalkanoyl chloride to a solution of the amino-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII in a suitable solvent, such as chloroform, at ambient temperature. The isolable intermediate chloroalkanesulfonamide or chloroalkanamide can then be treated with a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, at ambient temperature in a suitable solvent, such as DMF, to effect the cyclization.

Sulfamides of Formula XXIV, where R_{1b} is -X-N(R_8)-Q-R_4, and Q is –S(O)$_2$-N(R_8)-, can be prepared by reacting a compound or salt of Formula XXIII with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula HN(R_8)R_4. Alternatively, sulfamides of Formula XXIV can be prepared by reacting a compound of Formula XXIII with a sulfamoyl chloride of formula $R_4(R_8)N$-$S(O)_2Cl$. Many amines of Formula HN(R_8)R_4, and some sulfamoyl chlorides of Formula $R_4(R_8)N$-$S(O)_2Cl$ are commercially available; others can be prepared using known synthetic methods.

In steps (6) and (7) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIV is oxidized to afford a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXV, which is aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXa. Steps (6) and (7) of Reaction Scheme II can be carried out as described for steps (8) and (9), respectively, of Reaction Scheme I.

In step (8) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXa undergoes a palladium-catalyzed coupling reaction to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula IIb, which is a subgenus of Formulas I and II. The Suzuki coupling or Heck reaction can be carried out as described in step (10) of Reaction Scheme I.

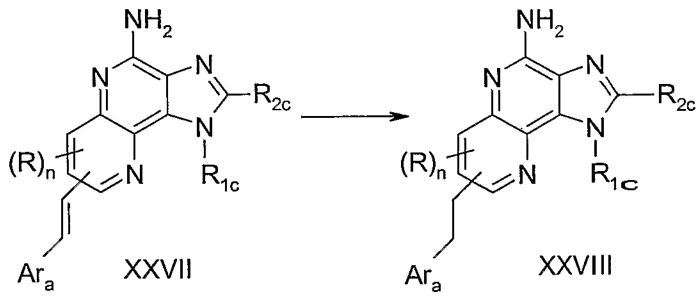
Reaction Scheme II



Compounds of the invention, wherein -Z- is ethylene, can be prepared as shown in Reaction Scheme III, wherein Ar_a, R, and n are as defined above; and R_{2c} and R_{1c} include R_{2a}, R_{1a}, and R_{1b} groups as defined above that are not subject to reduction under the conditions described in Reaction Scheme III. These groups include, for example, alkenyl and alkynyl groups.

In Reaction Scheme III, the vinyl group of a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXVII is reduced to provide an 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXVIII, which is a subgenus of Formulas I and II. Compounds of Formula XXVII can be prepared by the Suzuki coupling or the Heck reaction described in step (10) of Reaction Scheme I. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst, such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent, such as ethanol, methanol, or mixtures thereof.

Reaction Scheme III

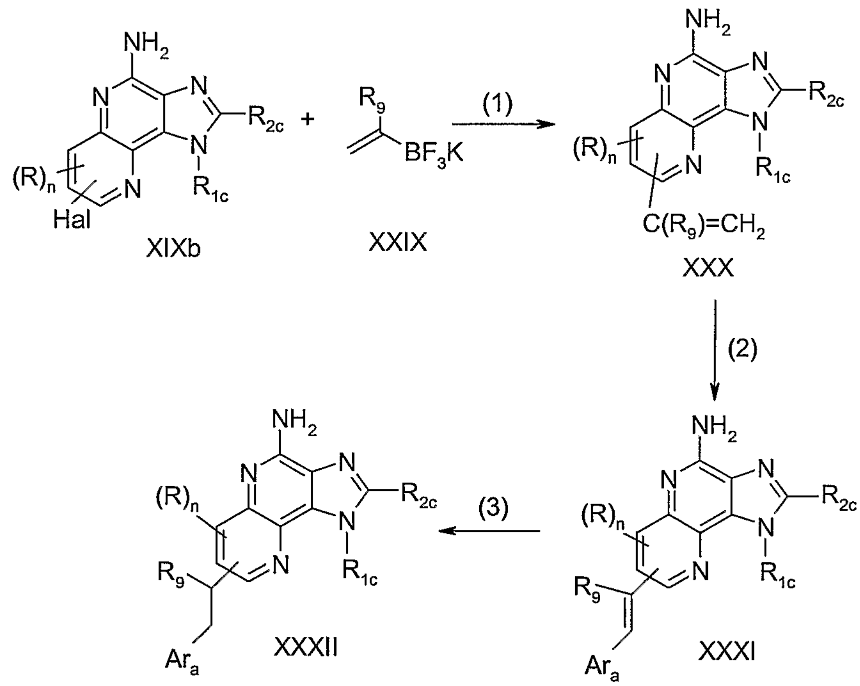


Palladium-catalyzed coupling reactions can also be used to prepare compounds of the invention according to Reaction Scheme IV, wherein R_{1c}, R_{2c}, R_9, R, Hal, Ar_a, and n are as defined above. In step (1) of Reaction Scheme IV, a halogen-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXb undergoes a Suzuki-type coupling with a potassium alkenyltrifluoroborate of Formula XXIX to provide a vinyl-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXX. The reaction is conveniently carried out by combining the compound of Formula XIXb and a compound of Formula XXIX, such as potassium vinyltrifluoroborate, in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct and a base, such as triethylamine, in a suitable solvent, such as *n*-propanol. The reaction can be carried out at an elevated temperature such as the reflux temperature of the solvent under an inert atmosphere.

In step (2) of Reaction Scheme IV, the Heck reaction is used to couple a vinylated 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXX with an aryl or hetereoaryl halide of Formula Ar_a-Hal or a trifluoromethanesulfonate of Formula Ar_a-OSO_2CF_3. Numerous compounds of Formula Ar_a-Hal are commercially available; others can be prepared using known synthetic methods. The reaction is conveniently carried out under the Heck reaction conditions described in step (10) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXI, which is a subgenus of Formulas I and II.

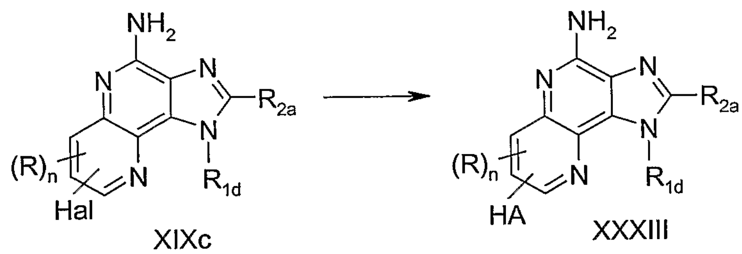
In step (3) of Reaction Scheme IV, the vinyl group of a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXI is reduced to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXII. The reaction is conveniently carried out by hydrogenation under the conditions described in Reaction Scheme III.

Reaction Scheme IV



Compounds of the invention can also be prepared according to Reaction Scheme V, wherein R, R_{2a}, Hal, and n are as defined above; R_{1d} includes groups defined by R_{1a} and R_{1b} described above; and HA is a heteroaryl group attached to the ring at a nitrogen atom. In Reaction Scheme V, a halogen-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXc undergoes a copper-catalyzed amination with a nitrogen-containing heteroaryl compound to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXIII, which is a subgenus of Formulas I and II. Several nitrogen-containing heteroaryl compounds, such as imidazole, pyrazole, and pyrrole, are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXc and the nitrogen-containing heteroaryl compound in the presence of copper (I) iodide, potassium phosphate, and *trans*-1,2-diaminocyclohexane in a suitable solvent, such as 1,4-dioxane. The reaction can be carried out at an elevated temperature, such as 110 °C.

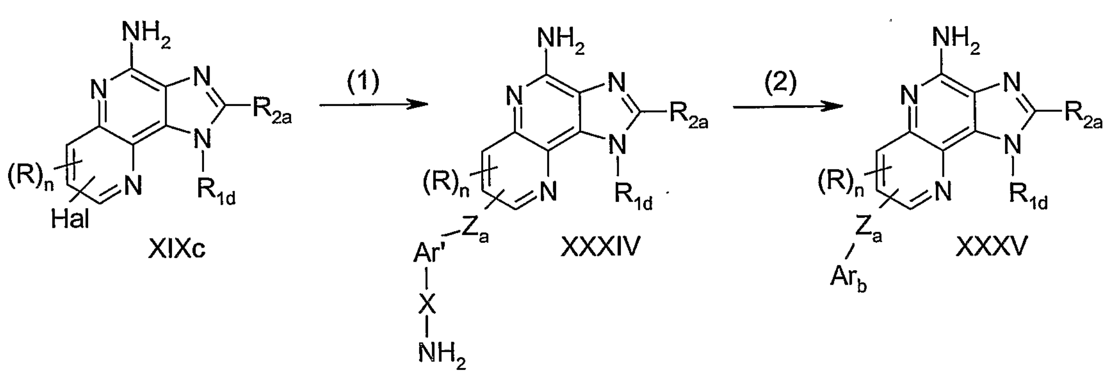
Reaction Scheme V



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme VI, wherein R, R_{1d}, R_{2a}, Ar', X, Hal, Z_a, and n are as defined above; and Ar_b is -Ar'-X-Y-R_4 or -Ar'-X-R_5, wherein Y, R_4, and R_5 are as defined above. In step (1) of Reaction Scheme VI, a halogen-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XIXc undergoes Suzuki coupling with a boronic acid of Formula NH_2-X-Ar'-Z_a-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula NH_2-X-Ar'-Z_a-B(O-alkyl)$_2$ to provide an 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXXIV, a subgenus of Formulas I and II. The reaction can be carried out according to one of the Suzuki coupling methods described in step (10) of Reaction Scheme I. Some reagents of Formula NH_2-X-Ar'-Z_a-$B(OH)_2$, anhydrides thereof, and NH_2-X-Ar'-Z_a-B(O-alkyl)$_2$ are commercially available; others can be prepared by known methods.

In step (2) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXIV is converted to a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXV, a subgenus of Formulas I and II, using one of the methods described in step (5) of Reaction Scheme II.

Reaction Scheme VI



Some amines of the Formula $H_2N\text{-}R_{1a}$, which are used in step (5) of Reaction Scheme I, can be made according to the following methods. For some embodiments, R_{1a} is a 1-hydroxycycloalkylmethyl group, a (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl group, or a group derived from a [1-(*tert*-butoxycarbonyl)-4-hydroxypiperidin-4-yl]methyl group. The corresponding amines of Formula $H_2N\text{-}R_{1a}$ can be prepared by combining a cyclic ketone, such as cyclopentanone, cyclobutanone, tetrahydro-4*H*-pyran-4-one, and *tert*-butyl 4-oxo-1-piperidinecarboxylate, with excess nitromethane in a suitable solvent, such as ethanol or methanol, in the presence of a catalytic amount of base, such as sodium ethoxide or sodium hydroxide, and reducing the resultant nitromethyl-substituted compound using conventional heterogeneous hydrogenation conditions. The hydrogenation is typically carried out in the presence of a catatlyst, such as palladium hydroxide on carbon, palladium on carbon, or Raney nickel, in a suitable solvent, such as ethanol. Both the reaction with nitromethane and the reduction can be carried out at room temperature. A wide variety of cyclic ketones can be obtained from commercial sources; others can be synthesized using known synthetic methods.

For some embodiments, R_{1a} is a 2-fluoro-2-methylpropyl group. The corresponding amine of Formula $H_2N\text{-}R_{1a}$ or a salt thereof can be prepared in three steps by (i) protecting the amino group of 1-amino-2-methylpropan-2-ol with a suitable protecting group such as a Boc group, (ii) converting the hydroxy group into a fluoro group, and (iii) deprotecting the amino group. The fluorination in step (ii) can be carried out by combining the protected amino alcohol with (diethylamino)sulfur trifluoride in a suitable solvent, such as dichloromethane. The reaction can be carried out at or below room temperature.

Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through VI. For example, position isomers of Formula XIX such as [1,6]naphthyridines, [1,7]naphthyridines, and [1,8]naphthyridines can be prepared according to the methods shown in Reaction Scheme I and can be used as starting materials in Reaction Schemes III through VI. In addition, steps in Reaction Schemes I and II may be carried out in a different order. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound wherein R_2 or R_1 is –X-OH (e.g. hydroxyalkyl) can be converted into a prodrug wherein R_2 or R_1

is, for example, $-X\text{-}O\text{-}C(R_6)\text{-}R_4$, $-X\text{-}O\text{-}C(R_6)\text{-}O\text{-}R_4$, or $-X\text{-}O\text{-}C(R_6)\text{-}N(R_8)\text{-}R_4$, wherein X, R_4, R_6, and R_8 are as defined above, using methods known to one skilled in the art. In addition, a compound wherein R is hydroxy may also be converted to an ester, an ether, a carbonate, or a carbamate. For any of these compounds containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C_{1-6} alkanoyloxymethyl, 1-(C_{1-6} alkanoyloxy)ethyl, 1-methyl-1-(C_{1-6} alkanoyloxy)ethyl, C_{1-6} alkoxycarbonyloxymethyl, *N*-(C_{1-6} alkoxycarbonyl)aminomethyl, succinoyl, C_{1-6} alkanoyl, α-aminoC_{1-4} alkanoyl, arylacyl, $-P(O)(OH)_2$, $-P(O)(O\text{-}C_{1-6}\text{ alkyl})_2$, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, and α-aminoacyl or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from racemic, D-, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydroylizable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as –C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")-R', –C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, or -CH(CH_3)Y_1; wherein R' and R" are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, or benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkyl, haloC_{1-4} alkoxy, $-O\text{-}C(O)\text{-}CH_3$, $-C(O)\text{-}O\text{-}CH_3$, $-C(O)\text{-}NH_2$, $-O\text{-}CH_2\text{-}C(O)\text{-}NH_2$, $-NH_2$, and $-S(O)_2\text{-}NH_2$, with the proviso that R" can also be hydrogen; each α-aminoacyl group is independently selected from racemic, D-, and L-amino acids; Y' is hydrogen, C_{1-6} alkyl, or benzyl; Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, or di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl; and Y_1 is mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl. For compounds containing an amine functional group,

particularly useful prodrugs are amides derived from carboxylic acids containing one to ten carbon atoms, amides dervied from racemic, D-, or L-amino acids, and carbamates containing one to ten carbon atoms.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce, and certain compounds or salts of the invention may inhibit, the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The

animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic

diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

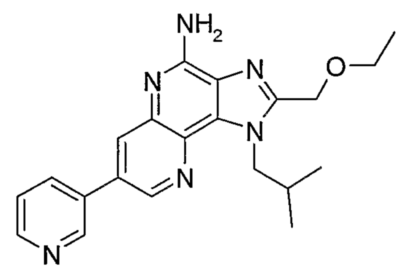
In the examples below automated flash chromatography was carried out using a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA). For some of these purifications, either a FLASH 40+M silica cartridge or a FLASH 65I silica cartridge (both available from Biotage, Inc, Charlottesville, Virginia, USA) was used. The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Preparation of 5-(*tert*-Butyldimethylsilanyloxymethyl)pyridine-3-boronic acid

3-Bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, *45*, 2832-2840 (2002)). Under a nitrogen atmosphere, a solution of 3-bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine (28.70 g, 94.94 mmol) and triisopropyl borate (26.3 mL, 114 mmol) in dry tetrahydrofuran was cooled to -70 °C. *n*-Butyllithium (45.6 mL, 114 mmol) was added dropwise over a period of 1.5 hours. The reaction was stirred for an additional 30 minutes and then allowed to warm to -20 °C. Dilute aqueous ammonium chloride was added, and the mixture was allowed to warm to ambient temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic fractions were concentrated under reduced pressure, and methanol was added to the resulting oil. A solid formed, which was stirred with water for two days, isolated by filtration, and dried under reduced pressure to provide 18.19 g of 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid as a white solid.

Example 1

2-(Ethoxymethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

A mixture of triethyl orthoformate (10 mL, 60.1 mmol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (40.9 g, 0.23 mol) (Meldrum's acid) was heated at 92 °C for 90 minutes and then cooled to 70 °C over one hour. 3-Amino-5-bromopyridine (40.9 g, 0.20 mol) was slowly added over 10 minutes with an ethanol rinse while maintaining the reaction temperature between 60 and 70 °C. The reaction was then heated for an additional 20 minutes and allowed to cool to room temperature. The reaction mixture was filtered and washed with ethanol (150 mL) yielding a tan solid. The solid was dried under vacuum for 2 hours to yield 59.14 g of 5-{[(5-bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione as a light yellow crystalline solid, mp 200-202 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (d, J = 14.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1 H), 8.62 (d, J = 14.3 Hz, 1H), 8.56(d, J = 1.9 Hz, 1H), 8.44-8.40 (m, 1H), 1.68 (s, 6H).

Part B

5-{[(5-Bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6–dione (59 g, 0.18 mol) was slowly added to DOWTHERM A heat transfer fluid (2000 mL) over a period of 5 minutes at 235-238 °C. Following addition, the reaction was maintained for an additional 5 minutes and then allowed to cool to 40 °C. A brown precipitate formed, which was filtered and washed with hexanes (150 mL). The brown solid was suspended in an ethanol/water mixture (90:10, 1500 mL), heated to a boil for 30 minutes, isolated by filtration, and washed with ethanol (200 mL) to yield 30.8 g of 7-bromo[1,5]naphthyridin-4-ol as a dark brown powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81(br s, 1H), 8.69(d, J = 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.95(d, J = 7.7 Hz, 1H), 6.22 (d, J = 7.5 Hz, 1H).

Part C

A mixture of 7-bromo[1,5]naphthyridin-4-ol (33 g, 0.147 mol) and fuming nitric acid (350 mL) was heated at reflux (90 °C internal reaction vessel temperature) for 3 hours. The reaction mixture was cooled to 50 °C, poured over 1 L of ice and neutralized to pH 2-3 with a solution of 50% aqueous NaOH. The resulting precipitate was filtered, washed with water, and dried over vacuum for 3 days to yield 25.1 g of 7-bromo-3-nitro[1,5]naphthyridin-4-ol as a yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.06(br s, 1H), 9.26(s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.37(d, J = 2.0 Hz, 1H).

Part D

Phosphorous oxychloride (16.76 g, 10.19 mL, 109.3 mmol) was added slowly dropwise to a suspension of 7-bromo-3-nitro[1,5]naphthyridin-4-ol (21.09 g, 78.1 mmol) in *N,N*-dimethylformamide (250 mL) (DMF) at ambient temperature and maintained overnight. The reaction mixture was then added to ice water (400 mL) with stirring. A solid precipitate formed, which was isolated by vacuum filtration and washed with water. The material was dried under high vacuum at ambient temperature overnight to yield 20.79 g of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine as a tan solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51(s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 9.02(d, J = 2.1 Hz,1H).

Part E

Triethylamine (17.97 mL, 129.0 mmol) was added to a solution of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (24.8 g, 86.0 mmol) in dichloromethane (200 mL) at 0 °C. Isobutylamine (9.40 mL, 94.6 mmol) was added dropwise to the mixture, and the mixture was stirred for 3 hours at ambient temperature. The reaction mixture was condensed under reduced pressure to a solid, which was triturated with water (200 mL). The precipitate was filtered, washed sequentially with water and hexanes, and dried to yield 27.5 g of 7-bromo-3-nitro[1,5]naphthyridin-4-yl-(2-methylpropyl)amine as a yellow powder, mp 114-115 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98(br s, 1H), 9.37(br s, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.39(d, J = 2.2 Hz, 1H), 4.36-4.01(br m, 2H), 2.06(heptet, J = 6.7 Hz, 1H), 1.09(d, J = 6.7, 6H). MS (APCI) m/z 325.2 and 327.2 $(M+H)^+$;

Anal. calcd for $C_{12}H_{13}BrN_4O_2$: C, 44.33; H, 4.03; N, 17.23. Found: C, 44.32; H, 3.81; N, 17.33.

Part F

A solution of sodium dithionite (77.95 g, 380.6 mmol) and potassium carbonate (58.35 g, 422.2 mmol) in water (250 mL) was added dropwise to a mechanically stirred solution of 7-bromo-3-nitro[1,5]naphthyridin-4-yl-(2-methylpropyl)amine (27.6 g, 84.6 mmol) and ethyl viologen dibromide (0.63 g, 1.7 mmol) in dichloromethane (300 mL) and water (50 mL). The reaction mixture was stirred overnight at ambient temperature. Water (500 mL) was added, and the reaction mixture was stirred for 10 minutes. The organic layer was separated and the aqueous layer was filtered through WHATMAN paper to remove insoluble material. The emulsion-free filtrate was extracted with dichloromethane, washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 22.3 g of 7-bromo-N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 2.2 Hz, 1H), 8.36(s, 1H), 8.33(d, J = 2.2 Hz, 1H), 6.03-5.89(br m, 1H), 3.66(br s, 2H), 3.27(t, J = 6.8, 2H), 1.83(heptet, J = 6.7 Hz, 1H), 1.00(d, J = 6.7 Hz, 6H).

Part G

A solution of 7-bromo-N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine (22.29 g, 75.51 mmol) in dichloromethane (300 mL) was cooled to 0 °C, and triethylamine (13.15 mL, 94.39 mmol) was added to the reaction mixture. Ethoxyacetyl chloride (11.56 g, 94.39 mmol) was added dropwise to the reaction mixture, and the reaction was maintained at ambient temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, triethylamine (52.62 mL, 377.6 mmol) and ethanol (250 mL) was added, and the resulting mixture was heated at reflux for 16 hours. The solvent was removed under reduced pressure and the residue was triturated with *n*-heptanes. The resulting precipitate was collected by filtration, washed with water, and dried. The product was then recrystallized from acetonitrile to yield 14 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as an off-white solid. The mother liquor was concentrated, and the residue was recrystallized from acetonitrile to yield an additional 2.37 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine. The *n*-heptanes fraction from the trituration was concentrated under reduced pressure, triturated with acetonitrile, and isolated by filtration to give an

additional 0.88 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine, for a total yield of 17.25 g of an off-white solid, mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33(s, 1H), 8.96(d, J = 2.2 Hz, 1H), 8.68(d, J = 2.2 Hz, 1H), 4.90(s, 2H), 4.78(d, J = 7.6 Hz, 2H), 3.64(q, J = 7.0 Hz, 2H), 2.47(heptet, J = 6.9 Hz, 1H), 1.26(t, J = 7.0, 3H), 0.98(d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 149.7, 147.2, 140.3, 139.3, 139.1, 134.5, 133.9, 117.9, 66.5, 65.3, 53.2, 29.7, 19.8, 15.0. MS (APCI) m/z 363.2 and 365.2 $(M+H)^+$;

Anal. calcd for $C_{16}H_{19}BrN_4O$: C, 52.90; H, 5.27; N, 15.42. Found: C, 52.93; H, 5.22; N, 15.55.

Part H

3-Chloroperoxybenzoic acid (77% pure, 17.11 g, 76.36 mmol) (mCPBA) was added to a stirred solution of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (13.87 g, 38.18 mmol) in dichloromethane (275 mL), and the reaction was stirred for 2 hours with additional mCPBA (2.91 g, 13.0 mmol) added after 1 hour. Ammonium hydroxide (90 mL) was added followed by addition of *p*-toluenesulfonyl chloride (9.10 g, 47.73 mmol) in small portions at 0 °C; the reaction was then allowed to warm to ambient temperature for 4 hours. The reaction mixture was filtered and then diluted with dichloromethane (300 mL) and a 4% solution of sodium carbonate (200 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to produce an orange solid. The crude product was triturated with acetonitrile to yield 8.4 g of a tan solid, which upon purification by automated flash chromatography (using a silica gel cartridge, eluting with chloroform:CMA, ranging in ratios from 100:0 to 80:20) to provide 7.03 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as an off-white solid, mp 163-164 °C.

^{1}H-NMR (300 MHz, DMSO) δ 8.57(d, J = 2.2 Hz, 1H), 8.10(d, J = 2.2 Hz, 1H), 7.15(br s, 2H), 4.77(s, 2H), 4.64(d, J = 7.6 Hz, 2H), 3.60(q, J = 7.0 Hz, 2H), 2.43-2.28(m, 1H), 1.16(t, J = 7.0, 3H), 0.89(d, J =6.7 Hz, 6H). MS (APCI) m/z 378.2 and 380.2 $(M+H)^+$.

Anal. calcd for $C_{16}H_{20}BrN_5O$: C, 50.80; H, 5.33; N, 18.51. Found: C, 50.62; H, 5.30; N, 18.52.

Part I

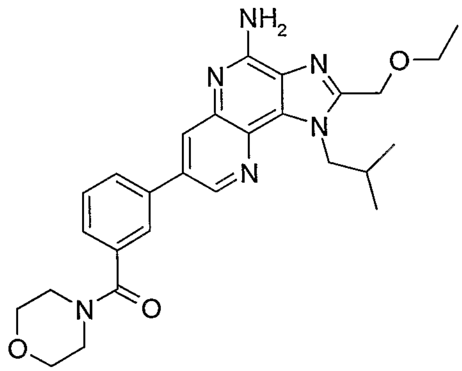
Pyridine-3-boronic acid (0.39 g, 3.2 mmol) was added to 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (1.0 g, 2.6 mmol) and 1-propanol (17 mL). The mixture was degassed and backfilled with nitrogen. Aqueous 2M sodium carbonate (1.6 mL), water (2 mL), triphenylphosphine (.021 g, 0.079 mmol), and palladium (II) acetate (0.0058 g, 0.026 mmol) were added to the reaction mixture followed by subsequent degassing. The mixture became homogenous upon heating at reflux for 1 hour. After an additional 1 hour of heating, the reaction was cooled to ambient temperature and extracted into chloroform. The resulting solution was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by automated flash chromatography (using a silica gel cartridge, eluting with CMA:chloroform ranging in ratios from 0:100 to 30:70) and concentrated under reduced pressure. The product was recrystallized from acetonitrile, filtered, and dried at 60 °C under vacuum to provide 0.66 g of 2-(ethoxymethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a white solid, mp 177-179 °C.

^{1}H NMR (300 MHz, DMSO) δ 9.07(m, 1H), 8.91(d, *J* = 2.2 Hz, 1H), 8.64(dd, *J* = 4.8, 1.6 Hz, 1H), 8.31-8.25(m, 1H), 8.22(d, *J* = 2.2 Hz, 1H), 7.58-7.51(m, 1H). 7.03 (br s, 2H), 4.80(s, 2H), 4.72(d, *J* = 7.6 Hz, 2H), 3.60(q, *J* = 7.0 Hz, 2H), 2.51-2.40(m, 1H), 1.18(t, *J* = 7.0 Hz, 3H), 0.92(d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, DMSO) δ 152.6, 150.1, 148.8, 147.8, 141.2, 140.2, 134.4, 133.2, 132.9, 132.5, 130.9, 129.9, 128.9, 123.9, 65.4, 63.9, 51.9, 29.1, 19.3, 14.8. MS (APCI) *m/z* 377.1 $(M+H)^+$;

Anal. calcd for $C_{21}H_{24}N_6O$: C, 67.00; H, 6.43; N, 22.32. Found: C, 66.82; H, 6.20; N, 22.36.

Example 2

2-(Ethoxymethyl)-1-(2-methylpropyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



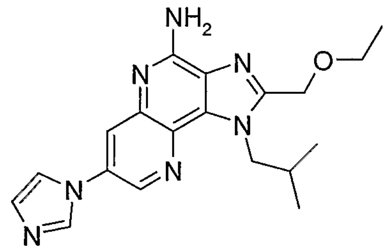
The general method of Part I of Example 1 was followed using 3-(morpholine-4-carbonyl)phenylboronic acid (0.745 g, 3.17 mmol) in lieu of pyridine-3-boronic acid. The crude reaction was purified automated flash chromatography (using a silica gel cartridge, eluting with CMA:chloroform ranging in ratios from 0:100 to 25:75). The combined clean fractions were concentrated under reduced pressure, recrystallized from acetonitrile, filtered, washed with acetonitrile and dried at 60 °C under vacuum to give 0.63 g of 2-(ethoxymethyl)-1-(2-methylpropyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a white solid, mp 185-187 °C.

^{1}H NMR (300 MHz, DMSO) δ 8.88(d, J = 2.2 Hz, 1H), 8.16(d, J = 2.2 Hz, 1H), 7.97-7.91(m, 1H), 7.89-7.84(m, 1H), 7.61(t, J = 7.7 Hz, 1H), 7.49-7.43(m, 1H). 6.98(br s, 2H), 4.79(s, 2H), 4.72(d, J = 7.5 Hz, 2H), 3.77-3.36(br abs, 8H), 3.60(q, J = 7.0 Hz, 2H), 2.50-2.38(m, 1H), 1.17(t, J = 7.0 Hz, 3H), 0.93(d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, DMSO) δ 168.6, 152.6, 150.0, 141.4, 140.3, 137.4, 136.5, 133.1, 133.0, 132.5, 129.8, 129.3, 128.8, 128.0, 126.4, 125.2, 65.9, 65.4, 63.9, 51.9, 47.7, 29.1, 19.3, 14.8. MS (APCI) *m/z* 489.2 $(M+H)^+$;

Anal. calcd for $C_{27}H_{32}N_6O_3$: C, 66.37; H, 6.60; N, 17.20. Found: C, 66.20; H, 6.68; N, 17.40.

Example 3

2-(Ethoxymethyl)-7-(imidazol-1-yl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Copper (I) iodide (0.06g, 0.53 mmol), potassium phosphate (1.18 g, 5.56 mmol), and imidazole (0.22 g, 3.17 mmol) were added to a glass tube. Sequential addition of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (1.0 g, 2.64 mmol), *trans*-1,2-diaminocyclohexane (0.06 g, 0.53 mmol) and dioxane (9 mL) followed. The tube was flushed with nitrogen, sealed, and heated to 110 °C, and the reaction mixture was stirred for 10 days. The reaction mixture was then diluted with a 1:1 mixture of chloroform and methanol (50 mL) and filtered through CELITE filter aid. The filtrate was concentrated under reduced pressure to give a black liquid, which was purified by automated flash chromatography (using a silica gel cartridge, eluting with CMA:chloroform ranging in ratios from 0:100 to 20:80), and concentrated under reduced pressure. The residue was recrystallized from diethyl ether to give 0.18 g of 2-(ethoxymethyl)-7-(imidazol-1-yl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a tan solid, mp 175-176 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 2H), 7.478-7.281 (m, 2H), 5.75 (br s, 2H), 4.84 (s, 2H), 4.74 (d, J = 7.6 Hz, 2H), 3.65 (q, J = 7.0 Hz, 2H), 2.559-2.407 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.00 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ153.0, 151.1, 141.5, 137.5, 134.2, 134.0, 132.7, 131.5, 124.9, 77.8, 77.4, 76.9, 66.9, 65.4, 53.4, 30.2, 20.2, 15.4. MS (ESI) *m/z* 366.3 $(M+H)^+$;

Anal. calcd for $C_{19}H_{23}N_7O$: C, 62.45; H, 6.34; N, 26.83. Found: C, 62.16; H, 6.20; N, 27.06.

Examples 4-58

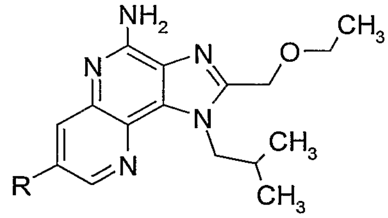
The compounds in the table below were prepared according to the following method. A solution of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-

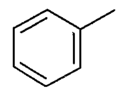
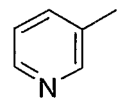
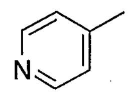
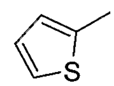
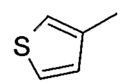
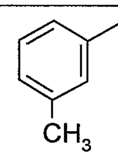
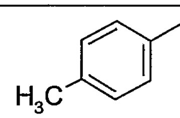
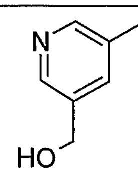
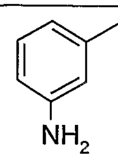
c][1,5]naphthyridin-4-amine (21.8 mg, 0.10 mmol) in 7:3 volume:volume (v:v) dichloromethane:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added, and the test tube was purged with nitrogen. The reaction mixture was sonicated until it had the consistency of milk. Palladium (II) acetate (0.292 mL of a 0.9 mol% solution in toluene, 0.0026 mmol), 2M aqueous sodium carbonate solution (600 μL), deionized water (113 μL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (52 μL, 0.00.78 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated to 80 °C overnight in a sand bath. For Example 11, the solvent was removed by vacuum centrifugation, and glacial acetic acid (3 mL), tetrahydrofuran (1 mL), and deionized water (1 mL) were added to the test tube. The reaction was heated for six hours at 60 °C.

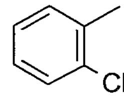
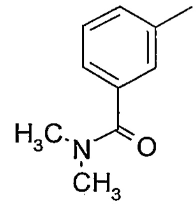
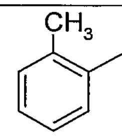
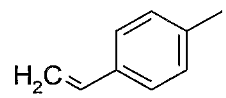
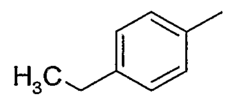
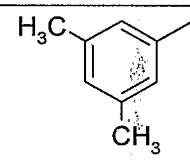
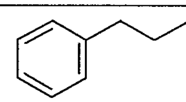
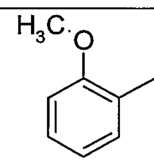
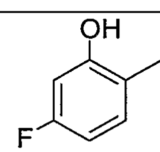
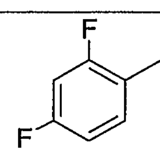
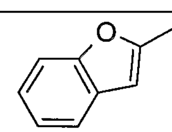
The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the following procedure. Hydrochloric acid (3 mL of 1 N in methanol) was added to adjust each example to pH 5-7, and the resulting solution was passed through the cartridge optionally using light nitrogen pressure. The cartridge was washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1% ammonia in methanol (2 x 5 mL) was then passed through the cartridge optionally using light nitrogen pressure, and the basic solution was collected and concentrated.

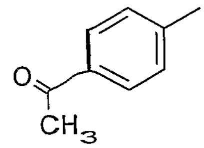
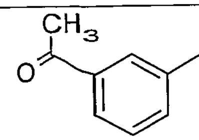
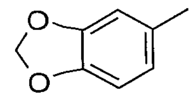
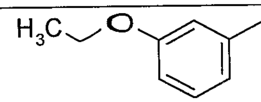
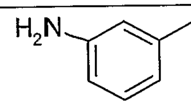
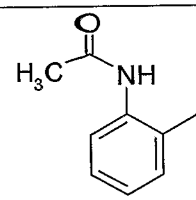
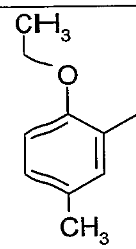
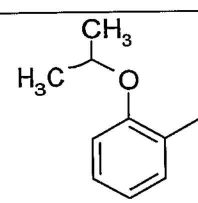
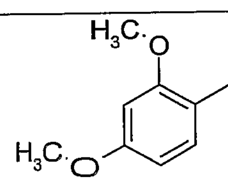
The compounds were purified by reversed phase preparative high-performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Zorbax BonusRP, 21.2 x 50 millimeters (mm), 5 micron particle size; non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

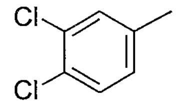
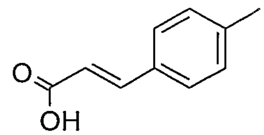
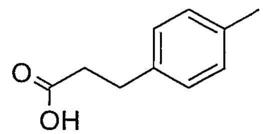
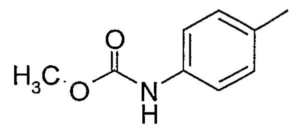
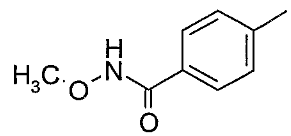
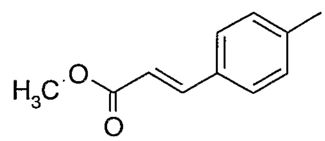
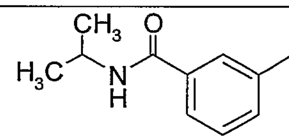
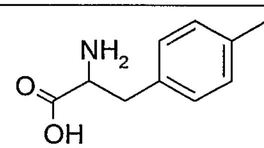
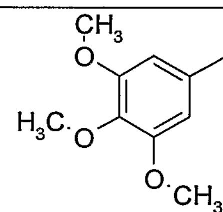
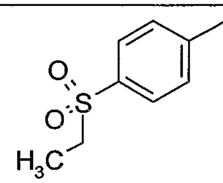
Examples 4-58

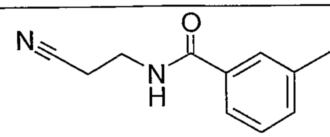
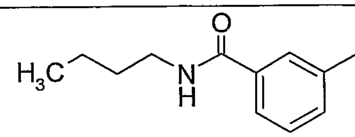
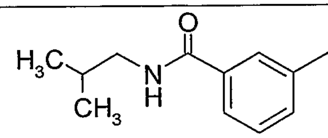
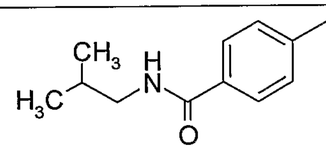
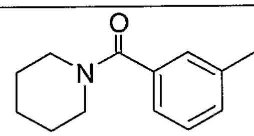
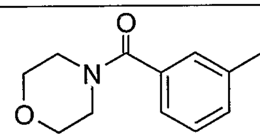
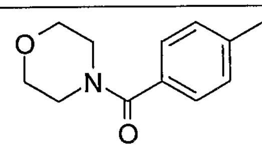
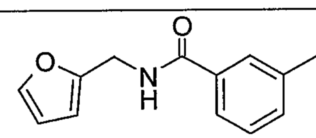
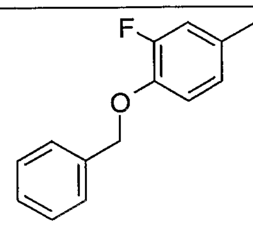


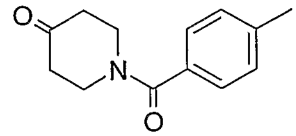
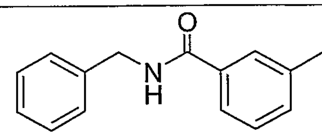
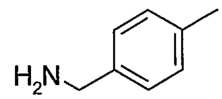
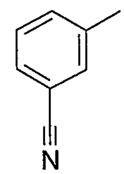
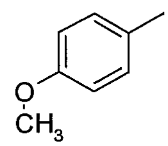
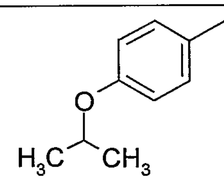
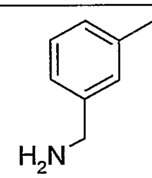
Example	Boronic acid	R	Measured Mass (M+H)
4	Phenylboronic acid		376.2146
5	Pyridine-3-boronic acid		377.2119
6	Pyridine-4-boronic acid		377.2121
7	Thiophene-2-boronic acid		382.1711
8	Thiophene-3-boronic acid		382.1700
9	3-Methylphenylboronic acid		390.2309
10	4-Methylphenylboronic acid		390.2287
11	5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		407.2219
12	3-Aminophenylboronic acid monohydrate		391.2284

13	2-Chlorophenylboronic acid		410.1754
14	3-(*N,N*-Dimethylamino-carbonyl)phenylboronic acid		447.2524
15	*o*-Tolylboronic acid		390.2317
16	4-Vinylphenylboronic acid		402.2272
17	4-Ethylphenylboronic acid		404.2445
18	3,5-Dimethylphenylboronic acid		404.2451
19	Phenethylboronic acid		404.2451
20	2-Methoxyphenylboronic acid		406.2242
21	(4-Fluoro-2-hydroxy)phenylboronic acid		410.1995
22	2,4-Difluorophenylboronic acid		412.1924
23	Benzo[B]furan-2-boronic acid		416.2080

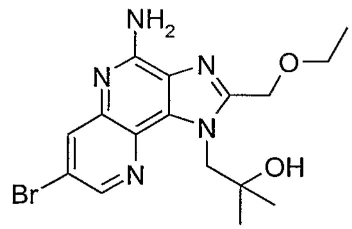
24	4-Acetylphenylboronic acid		418.2242
25	3-Acetylphenylboronic acid		418.2247
26	3,4-Methylenedioxyphenylboronic acid		420.2025
27	3-Ethoxyphenylboronic acid		420.2388
28	3-Aminophenylboronic acid hydrochloride		391.2283
29	(2-Acetylaminophenyl)boronic acid		433.2321
30	2-Ethoxy-5-methylphenylboronic acid		434.2546
31	2-Isopropoxyphenylboronic acid		434.2542
32	2,4-Dimethoxyphenylboronic acid		436.2352

33	3,4-Dichlorophenylboronic acid		444.1331
34	4-(2-Carboxyvinyl)phenylboronic acid		446.2193
35	3-(4-Boronophenyl)propionic acid		448.2319
36	4-(Methoxycarbonyl-amino)phenylboronic acid		449.2280
37	4-(*O*-Methylhydroxylaminocarbonyl)-phenylboronic acid		449.2285
38	[4-(*E*-3-Methoxy-3-oxo-1-propen-1-yl)phenyl]boronic acid		460.2364
39	3-(*N*-Isopropylamino-carbonyl)phenylboronic acid		461.2662
40	4-Borono-*DL*-phenylalanine		463.2442
41	3,4,5-Trimethoxyphenylboronic acid		466.2456
42	4-(Ethylsulfonyl)phenylboronic acid		468.2053

43	3-(2-Cyanoethylamino-carbonyl)phenylboronic acid		472.2439
44	3-(Butylamino-carbonyl)phenylboronic acid		475.2809
45	3-(Isobutylamino-carbonyl)phenylboronic acid		475.2811
46	4-(Isobutylamino-carbonyl)phenylboronic acid		475.2798
47	3-(Piperidine-1-carbonyl)phenylboronic acid		487.2775
48	3-(Morpholine-4-carbonyl)phenylboronic acid		489.2620
49	4-(Morpholine-4-carbonyl)phenylboronic acid		489.2597
50	3-(Furfurylamino-carbonyl)phenylboronic acid		499.2435
51	4-Benzyloxy-3-fluorophenylboronic acid		500.2449

52	4-(4-Oxopiperidine-1-carbonyl)phenylboronic acid		501.2581
53	3-(*N*-Benzylamino-carbonyl)phenylboronic acid		509.2629
54	(4-Aminomethyl-phenyl)boronic acid, pinacol ester hydrochloride		405.2411
55	3-Cyanophenylboronic acid		401.2065
56	4-Methoxyphenylboronic acid		406.2264
57	4-Isopropoxyphenylboronic acid		434.2543
58	(3-Aminomethyl-phenyl)boronic acid hydrochloride		405.2431

Preparation of 1-[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol



Part A

A mixture of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (92.5 g, 321 mmol) and dichloromethane (1.5 L) was cooled to 10 °C. 1-Amino-2-methylpropan-2-ol (63.01 g, 707 mmol) was added dropwise over a period of 30 minutes; during the addition, the reaction temperature did not rise above 13 °C. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The solvent was removed under reduced pressure, and the solid residue was mixed with deionized water (200 mL). The solid was isolated by filtration, washed with deionized water (2 x 200 mL), and dried in a vacuum oven overnight at 35 °C to provide 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol.

Part B

The material from Part A was added to a Parr vessel followed by methanol (1.13 L) and acetonitrile (2.26 L). The vessel was purged with nitrogen, and 5% platinum on carbon (3.4 g), which had been wet with acetonitrile, was added. The reaction mixture was placed under hydrogen pressure (50 psi, 3.4×10^5 Pa) overnight and filtered. The filtrate was concentrated under reduced pressure to provide 103 g of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow solid.

Part C

A mixture of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (100.0 g, 321.4 mmol) and acetonitrile (1 L) was stirred for five minutes and ethoxyacetyl chloride (43.3 g, 353.3 mmol) was added. The reaction was stirred overnight at room temperature. The solid product was isolated by filtration and washed with acetonitrile (200 mL) to provide 113 g of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-2-ethoxyacetamide hydrochloride as a yellow solid.

Part D

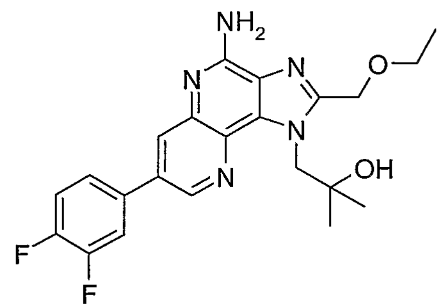
Potassium carbonate (113 g) and deionized water (565 mL) were sequentially added to a solution of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-2-ethoxyacetamide hydrochloride (113 g, 261 mmol) in denatured ethanol (1.695 L), and the resulting mixture was heated at reflux (77 °C) overnight and allowed to cool to room temperature. The ethanol was removed under reduced pressure, and the resulting mixture was filtered to isolate a solid. The solid was washed with deionized water (100 mL) and dried over two nights in a vacuum oven at 40 °C to provide 90 g of 1-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a brown solid. Material from a separate run was used in the next step.

Part E

mCPBA (35.5 g of 77% purity, 158 mmol) was added to a stirred solution of 1-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (15 g, 0.040 mol) in chloroform (400 mL), and the reaction was stirred at room temperature for 2.5 hours. Concentrated ammonium hydroxide (200 mL) was added, and then *p*-toluenesulfonyl chloride (18.9 g, 98.9 mmol) was added over a period of five minutes. The reaction mixture was stirred at room temperature for 2.5 hours, and an analysis by liquid chromatography/mass spectrometry (LC/MS) indicated the presence of starting material. Additional *p*-toluenesulfonyl chloride (11 g) was added, and the reaction mixture was stirred at room temperature for one hour. An analysis by LC/MS indicated the reaction was still incomplete. Additional ammonium hydroxide (100 mL) and *p*-toluenesulfonyl chloride (10 g) were added, and the mixture was stirred for 30 minutes at room temperature. The aqueous layer was separated and extracted with dichloromethane (2 x 300 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue (41.4 g) was purified by automated flash chromatography (FLASH 65I cartridge, eluting with ethyl acetate:methanol in a gradient from 97:3 to 85:15) to provide 5.96 g of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a yellow solid.

Example 59

1-[4-Amino-7-(3,4-difluorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

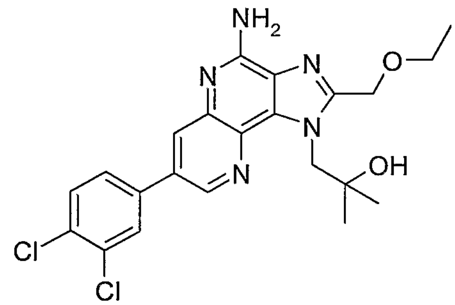


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.4 g, 3.55 mmol), 3,4-difluorophenylboronic acid (1.12 g, 7.10 mmol), potassium carbonate (1.62 g, 11.7 mmol), 1,2-dimethyoxyethane (DME) (13 mL), and water (7 mL) was stirred under nitrogen. Dichlorobis(triphenylphosphine)palladium(II) (0.025 g, 0.036 mmol) was added, and the suspension was heated at reflux for five hours, allowed to cool to room temperature, diluted with water (20 mL), and extracted with dichloromethane (50 mL). An emulson formed. Solid sodium chloride was added to saturate the aqueous layer. The organic layer was then removed under reduced pressure. The aqueous layer was extracted with dichloromethane (4 x 50 mL); the third extraction was allowed to stand overnight. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid (2.03 g) was dissolved in dichloromethane (45 mL), purified by automated flash chromatography (40+M silica cartridge, eluting with 3% to 10% methanol in ethyl acetate), and then triturated with acetonitrile. The resulting solid was isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 485 mg of 1-[4-amino-7-(3,4-difluorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as an off-white solid, mp 193-195 °C.

Anal. calcd for $C_{22}H_{23}F_2N_5O_2$: C, 61.82; H, 5.42; N, 16.38. Found: C, 61.95; H, 5.46; N, 16.34.

Example 60

1-[4-Amino-7-(3,4-dichlorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

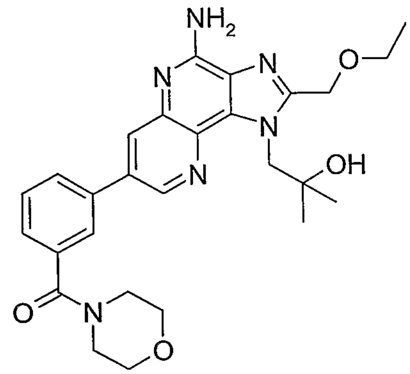


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.4 g, 3.55 mmol), 3,4-difluorophenylboronic acid (1.36 g, 7.10 mmol), potassium carbonate (1.62 g, 11.7 mmol), DME (13 mL), and water (7 mL) was stirred under nitrogen. Dichlorobis(triphenylphosphine)palladium(II) (0.025 g, 0.036 mmol) was added, and the suspension was heated at reflux for five hours and allowed to cool to room temperature. The DME was removed under reduced pressure, and the resulting mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 50 mL). An emulson formed; the second extraction was allowed to stand overnight. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid (2.2 g) was dissolved in dichloromethane (15 mL), purified as described in Example 59 to provide 264 mg of 1-[4-amino-7-(3,4-dichlorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as an off-white solid, mp 144-147 °C.

Anal. calcd for $C_{22}H_{23}Cl_2N_5O_2$: C, 57.40; H, 5.04; N, 15.21. Found: C, 57.11; H, 5.07; N, 14.99.

Example 61

1-{4-Amino-2-(ethoxymethyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol

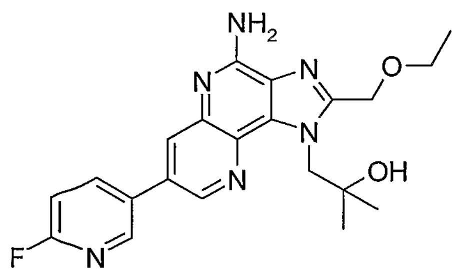


Under a nitrogen atmosphere, a suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.5 g, 3.8 mmol), 3-(morpholine-4-carbonyl)phenylboronic acid (1.07 g, 4.57 mmol), potassium carbonate (1.74 g, 12.6 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.027 g, 0.038 mmol), DME (13 mL), and water (7 mL) was stirred in a pressure vessel. The vessel was sealed, and the suspension was heated at 110 °C for 22 hours and allowed to cool to room temperature. The DME was removed under reduced pressure, and the resulting mixture was extracted with dichloromethane (3 x 25 mL) and ethyl acetate (25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting tan solid (2.11 g) was dissolved in dichloromethane (15 mL), purified by automated flash chromatography (40+M silica cartridge, eluting with 5% to 20% methanol in ethyl acetate). The resulting foamy solid was concentrated twice from methyl acetate, and the resulting solid was triturated with acetonitrile, isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 601 mg of 1-{4-amino-2-(ethoxymethyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as a white solid, mp 149-152 °C.

Anal. calcd for $C_{27}H_{32}N_6O_4$: C, 64.27; H, 6.39; N, 16.66. Found: C, 64.13; H, 6.62; N, 16.68.

Example 62

1-[4-Amino-2-(ethoxymethyl)-7-(6-fluoropyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

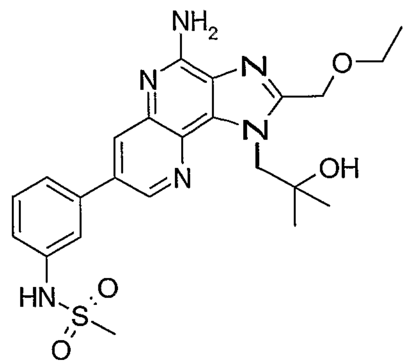


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.4 g, 3.55 mmol), 6-fluoropyridine-3-boronic acid (0.597 g, 4.26 mmol), potassium carbonate (1.62 g, 11.7 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.025 g, 0.036 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere and then heated at 110 °C for 17.5 hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure, and the residue was partitioned between water (25 mL) and dichloromethane (25 mL). A solid was present in the organic layer, and methanol was added to dissolve the solid. The aqueous layer was extracted with dichloromethane (3 x 20 mL). Silica gel was added to the combined organic fractions, and the mixture was concentrated under reduced pressure. The residue was purified by automated flash chromatography (40+M silica cartridge, eluting with 5% to 15% methanol in ethyl acetate) followed by recrystallization from acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 530 mg of 1-[4-amino-2-(ethoxymethyl)-7-(6-fluoropyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as white crystals, mp 218-220 °C.

Anal. calcd for $C_{21}H_{23}FN_6O_2$: C, 61.45; H, 5.65; N, 20.47. Found: C, 61.35; H, 5.55; N, 20.72.

Example 63

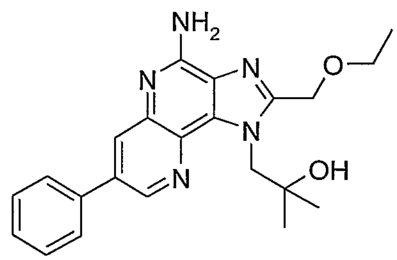
N-{3-[4-Amino-2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]phenyl}methanesulfonamide



A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.4 g, 3.55 mmol), (3-methylsulfonylaminophenyl)boronic acid (0.916 g, 4.26 mmol), potassium carbonate (1.62 g, 11.7 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.025 g, 0.036 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere and then heated at 110 °C for 18.5 hours and allowed to cool to room temperature. An analysis by LC/MS indicated the reaction was incomplete, and additional (3-methylsulfonylaminophenyl)boronic acid (1.0 g) and dichlorobis(triphenylphosphine)palladium(II) (0.15 g) were added. The reaction was heated at 110 °C for six hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure. The entire reaction mixture was diluted with methanol, and silica gel was added. The mixture was concentrated under reduced pressure. The residue was purified by chromatography according to the method described in Example 62 followed by crystallization from methyl acetate (20 mL). The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 679 mg of *N*-{3-[4-amino-2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]phenyl}methanesulfonamide as yellow crystals, mp 206-208 °C. Anal. calcd for $C_{23}H_{28}N_6O_4S$: C, 57.01; H, 5.82; N, 17.34. Found: C, 56.96; H, 5.82; N, 16.99.

Example 64

1-[4-Amino-2-(ethoxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

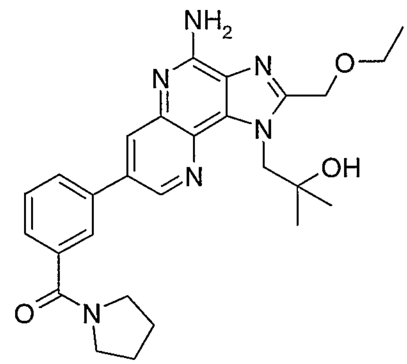


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.55 g, 3.93 mmol), phenylboronic acid (0.575 g, 4.72 mmol), potassium carbonate (1.79 g, 13.0 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.028 g, 0.039 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere and then heated at reflux for 61 hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure. The residue was diluted with methanol, and silica gel was added. The mixture was concentrated under reduced pressure. The residue was purified by chromatography according to the method described in Example 59. The resulting foamy solid (1.55 g) was concentrated twice from acetonitrile and then triturated with acetonitrile (25 mL) to provide a solid. The solid was isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 65 °C to provide 887 mg of 1-[4-amino-2-(ethoxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as an off-white solid, mp 158-159 °C.

Anal. calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.27; H, 6.66; N, 18.08.

Example 65

1-{4-Amino-2-(ethoxymethyl)-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol

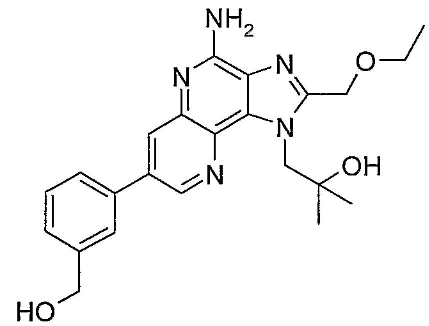


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.2 g, 3.0 mmol), (3-pyrrolidinylcarbonylphenyl)boronic acid (0.800 g, 3.65 mmol), potassium carbonate (1.4 g, 10.0 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.021 g, 0.030 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere in a pressure vessel. The vessel was then sealed and heated at 110 °C for 16.5 hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure. The residue was diluted with methanol, and silica gel was added. The mixture was concentrated under reduced pressure. The residue was purified by automated flash chromatography (FLASH 40+M silica cartridge, eluting with 10% to 25% methanol in ethyl acetate). The resulting material was concentrated twice from acetonitrile and then triturated with acetonitrile (100 mL) to provide a solid. The solid was isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 65 °C to provide 403 mg of 1-{4-amino-2-(ethoxymethyl)-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as a white solid, mp 185-187 °C.

Anal. calcd for $C_{27}H_{32}N_6O_3$: C, 66.37; H, 6.60; N, 17.20. Found: C, 66.26; H, 6.53; N, 17.26.

Example 66

1-{4-Amino-2-(ethoxymethyl)-7-[3-(hydroxymethyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

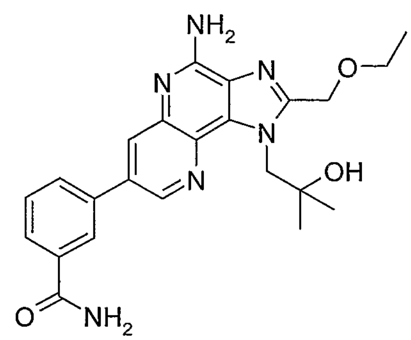


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.2 g, 3.0 mmol), 3-(hydroxymethyl)benzeneboronic acid (0.555 g, 3.65 mmol), potassium carbonate (1.4 g, 10.0 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.021 g, 0.030 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere in a pressure vessel. The vessel was then sealed and heated at 110 °C for 16.5 hours and allowed to cool to room temperature. The volatiles were removed under reduced pressure. The residue was diluted with methanol, and silica gel was added. The mixture was concentrated under reduced pressure. The residue was purified by automated flash chromatography (FLASH 40+M silica cartridge, eluting with 5% to 20% methanol in ethyl acetate) followed by trituration with acetonitrile. The resulting solid was isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 65 °C to provide 449 mg of 1-{4-amino-2-(ethoxymethyl)-7-[3-(hydroxymethyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a white solid, mp 186-187 °C.

Anal. calcd for $C_{23}H_{27}N_5O_3$: C, 65.54; H, 6.46; N, 16.62. Found: C, 65.47; H, 6.31; N, 16.67.

Example 67

3-[4-Amino-2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]benzamide

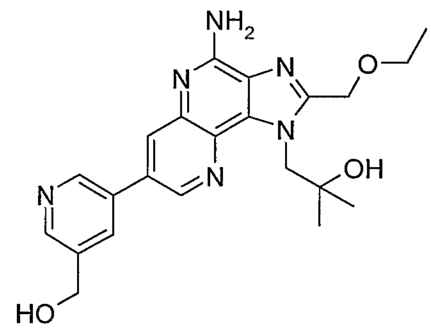


A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.2 g, 3.0 mmol), (3-aminocarbonylphenyl)boronic acid (0.603 g, 3.65 mmol), potassium carbonate (1.4 g, 10.0 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.021 g, 0.030 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere in a pressure vessel. The vessel was then sealed and heated at 110 °C for 64 hours and allowed to cool to room temperature. A precipitate formed and was isolated by filtration, washed with water and DME, and recrystallized from methanol (100 mL/900 mg). The crystals were isolated by filtration, washed with methanol, and dried in a vacuum oven at 65 °C to provide 191 mg of 3-[4-amino-2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]benzamide as an off-white solid, mp >250 °C.

Anal. calcd for $C_{23}H_{26}N_6O_3$: C, 63.58; H, 6.03; N, 19.34. Found: C, 63.57; H, 6.16; N, 19.38.

Example 68

1-{4-Amino-2-(ethoxymethyl)-7-[5-(hydroxymethyl)pyridin-3-yl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol



Part A

A suspension of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.5 g, 3.80 mmol), 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid (1.22 g, 4.57 mmol), potassium carbonate (1.74 g, 12.6 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.027 g, 0.038 mmol), DME (13 mL), and water (7 mL) was stirred under a nitrogen atmosphere and then heated at 110 °C in a pressure vessel for 6 hours and allowed to cool to room temperature. An analysis by LC/MS indicated the reaction was incomplete, and additional dichlorobis(triphenylphosphine)palladium(II) (0.035 g) was added. The reaction was heated at 110 °C for 16 hours and allowed to cool to room temperature. The DME was removed under reduced pressure, and the resulting mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid was dissolved in dichloromethane (15 mL) purified by chromatography according to the method described in Example 62 to provide 1.37 g of 1-{4-amino-7-[5-(*tert*-butyldimethylsilanyloxymethyl)pyridin-3-yl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a yellow solid.

Part B

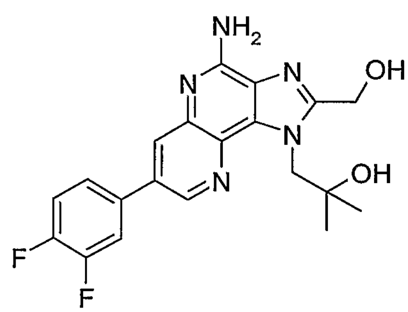
A solution of 1-{4-amino-7-[5-(*tert*-butyldimethylsilanyloxymethyl)pyridin-3-yl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.37 g, 2.55 mmol) in acetic acid (10 mL), tetrahydrofuran (10 mL), and water (10 mL) was stirred at 60 °C for 18.5 hours and allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was diluted with saturated aqueous

sodium bicarbonate (30 mL). Dichloromethane was added, but an oil was present that remained insoluble in both phases. Both phases were decanted away from the oil, which was dissolved in methanol. The aqueous phase was then separated and extracted with dichloromethane (30 mL) and ethyl acetate (2 x 30 mL). Silica gel was added to the combined dichloromethane, ethyl acetate, and methanol fractions, and the solvent was removed under reduced pressure. The residue was purified by automated flash chromatography (FLASH 40+M silica cartridge, eluting with 5% to 20% methanol in dichloromethane). The resulting material was concentrated from acetonitrile to form a solid, which was triturated with acetonitrile (30 mL), isolated by filtration, washed with acetonitrile, and dried overnight in a vacuum oven to provide 530 mg of 1-{4-amino-2-(ethoxymethyl)-7-[5-(hydroxymethyl)pyridin-3-yl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as a light yellow solid, mp 212-214 °C.

Anal. calcd for $C_{22}H_{26}N_6O_3$: C, 62.54; H, 6.20; N, 19.89. Found: C, 62.39; H, 6.09; N, 19.91.

Example 69

1-[4-Amino-7-(3,4-difluorophenyl)-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol



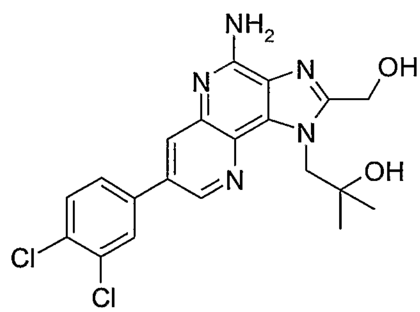
A suspension of 1-[4-amino-7-(3,4-difluorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (0.790 g, 1.85 mmol), obtained from the filtrate from the trituration in Example 59, in dichloromethane (20 mL) was cooled to 0 °C. Boron tribromide (5.54 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was stirred at room temperature for 22.5 hours. An analysis by LC/MS indicated the reaction was incomplete, and additional boron tribromide (2.7 mL) was added. The reaction was stirred for three hours at room temperature, and then methanol (25 mL) was carefully added. The resulting solution was stirred at room

temperature for one hour and concentrated under reduced pressure. A solution of ammonia in methanol (30 mL of 2 M) was added, and the mixture was stirred for 30 minutes and then diluted with methanol (50 mL) and dichloromethane (50 mL). Silica gel was added, and the mixture was concentrated under reduced pressure. The residue was purified by chromatography according to the method described in Example 62. The resulting solid was triturated with acetonitrile, isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 269 mg of 1-[4-amino-7-(3,4-difluorophenyl)-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a light yellow solid, mp 256-258 °C.

Anal. calcd for $C_{20}H_{19}F_2N_5O_2$: C, 60.15; H, 4.80; N, 17.53. Found: C, 60.15; H, 4.74; N, 17.80.

Example 70

1-[4-Amino-7-(3,4-dichlorophenyl)-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

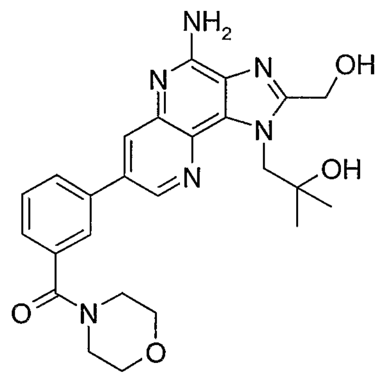


A solution of 1-[4-amino-7-(3,4-dichlorophenyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (0.850 g, 1.85 mmol), obtained from the filtrate from the trituration in Example 60, in dichloromethane (20 mL) was cooled to 0 °C. Boron tribromide (5.5 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was stirred at room temperature for 24 hours. An analysis by LC/MS indicated the reaction was incomplete, and additional boron tribromide (5.5 mL) was added. The reaction was stirred for three hours at room temperature, and the work-up and purification procedures described in Example 69 were followed to provide 233 mg of 1-[4-amino-7-(3,4-dichlorophenyl)-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol, mp 254-256 °C.

Anal. calcd for $C_{20}H_{19}Cl_2N_5O_2$: C, 55.57; H, 4.43; N, 16.20. Found: C, 55.50; H, 4.58; N, 16.01.

Example 71

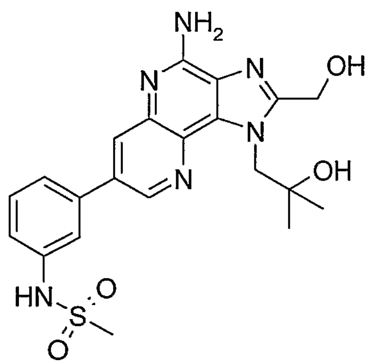
1-{4-Amino-2-(hydroxymethyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol



A solution of 1-{4-amino-2-(ethoxymethyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol (1.10 g, 2.18 mmol), obtained from the filtrate from the trituration in Example 61, in dichloromethane (20 mL) was cooled to -78 °C. Boron tribromide (10.9 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for 5.5 hours. Methanol (20 mL) was carefully added, and the resulting solution was stirred at room temperature for one hour and concentrated under reduced pressure. A solution of ammonia in methanol (50 mL of 1 M) was added, and the mixture was stirred for one hour. Silica gel was added, and the mixture was concentrated under reduced pressure. The resulting mixture was purified according to the methods described in Example 61 with the modification that chromatographed material was concentrated from acetonitrile instead of methyl acetate. 1-{4-Amino-2-(hydroxymethyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol (307 mg) was obtained as a light yellow solid, mp 153-155 °C.
Anal. calcd for $C_{25}H_{28}N_6O_4$: C, 63.01; H, 5.92; N, 17.64. Found: C, 62.92; H, 5.67; N, 17.51.

Example 72

N-{3-[4-Amino-2-(hydroxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]phenyl}methanesulfonamide

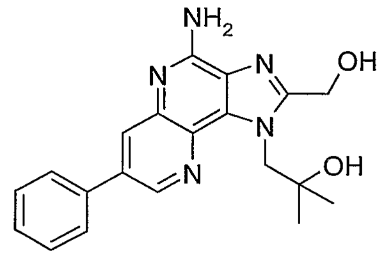


A suspension of *N*-{3-[4-amino-2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]phenyl}methanesulfonamide (1.17 g, 2.41 mmol), obtained from the filtrate from the recrystallization in Example 63, in dichloromethane (20 mL) was cooled to 0 °C. Boron tribromide (12.1 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was stirred at room temperature for 22 hours. Methanol (40 mL) was carefully added, and the resulting solution was stirred at room temperature for one hour and concentrated under reduced pressure. A solution of ammonia in methanol (100 mL of 1 M) was added, and the mixture was stirred at room temperature and then concentrated under reduced pressure. The residue was triturated with methanol (50 mL), and the resulting solid was isolated by filtration and washed with methanol and acetonitrile. The solid (710 mg) was then recrystallized from acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 493 mg of *N*-{3-[4-amino-2-(hydroxymethyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]phenyl}methanesulfonamide as a yellow solid, mp > 250 °C.

Anal. calcd for $C_{21}H_{24}N_6O_4S$: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.99; H, 5.06; N, 18.26.

Example 73

1-[4-Amino-2-(hydroxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

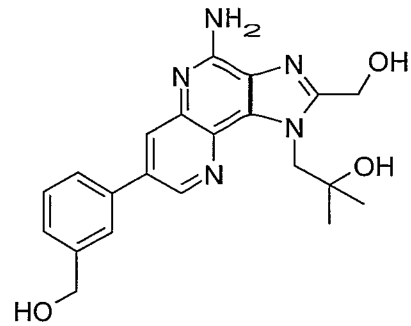


A solution of 1-[4-amino-2-(ethoxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (1.0 g, 2.55 mmol), obtained from the filtrate from the trituration in Example 64, in dichloromethane (25 mL) was cooled to 0 °C. Boron tribromide (12.8 mL of a 1 M solution in dichloromethane) was added dropwise, and the resulting suspension was stirred at room temperature for 14.5 hours. Methanol (50 mL) was carefully added, and the resulting solution was stirred at room temperature for one hour and concentrated under reduced pressure. A solution of ammonia in methanol (50 mL of 1 M) was added, and the suspension was stirred at room temperature for three hours. A solid was isolated by filtration, washed with methanol and acetonitrile, and dried in a vacuum oven at 65 °C to provide 403 mg of 1-[4-amino-2-(hydroxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a white solid, mp 244-245 °C.

Anal. calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 65.90; H, 5.77; N, 19.34.

Example 74

1-{4-Amino-2-(hydroxymethyl)-7-[3-(hydroxymethyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol

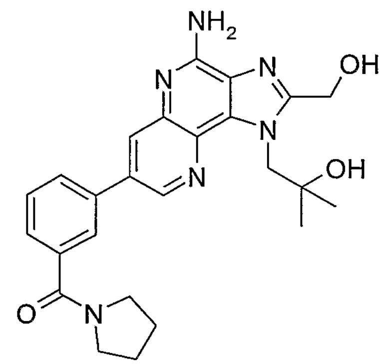


A suspension of 1-{4-amino-2-(ethoxymethyl)-7-[3-(hydroxymethyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (0.800 g, 1.90 mmol) obtained from the filtrate from the trituration in Example 66, in dichloromethane (20 mL) was cooled to 0 °C. Boron tribromide (9.5 mL of a 1 M solution in dichloromethane) was added dropwise, and the resulting suspension was stirred at room temperature for 15 hours. Methanol was carefully added, and the resulting solution was stirred at room temperature for one hour and concentrated under reduced pressure. The residue (1.33 g) was dissolved in DMF (15 mL), and potassium acetate was added. The mixture was heated at 50 °C for 18 hours and then concentrated under reduced pressure. The residue was dissolved in methanol (20 mL) and water (10 mL), and lithium hydroxide monohydrate (1.5 g) was added. The reaction was stirred at room temperature for 64 hours and concentrated under reduced pressure. Methanol and silica gel were added, and the mixture was concentrated under reduced pressure. The residue was purified by automated flash chromatography (FLASH 40+M cartridge, eluting with 7% to 20% 1 M methanolic ammonia in dichloromethane) followed by recrystallization from acetonitrile after a hot filtration. The crystals were washed with acetonitrile and dried in a vacuum oven at 65 °C to provide 146 mg of 1-{4-amino-2-(hydroxymethyl)-7-[3-(hydroxymethyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a yellow solid, mp 227-229 °C.

Anal. calcd for $C_{21}H_{23}N_5O_3 \cdot 0.1H_2O$: C, 63.82; H, 5.92; N, 17.72. Found: C, 63.62; H, 5.93; N, 17.79.

Example 75

1-{4-Amino-2-(hydroxymethyl)-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol

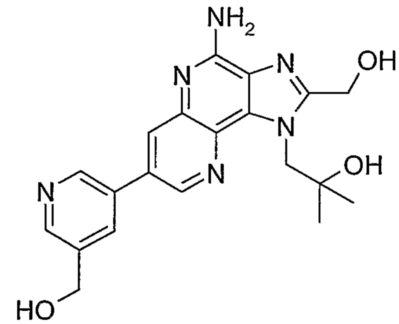


A solution of 1-{4-amino-2-(ethoxymethyl)-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol (1.0 g, 2.0 mmol), obtained from the filtrate from the trituration in Example 65, in dichloromethane (20 mL) was cooled to 0 °C. Boron tribromide (10.2 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for 15 hours. Methanol (50 mL) was carefully added, and the resulting solution was stirred at room temperature for one hour and concentrated under reduced pressure. A solution of ammonia in methanol (50 mL of 1 M) was added, and the mixture was stirred for one hour. Silica gel was added, and the mixture was concentrated under reduced pressure. The resulting mixture was purified by automated flash chromatography (FLASH 40+M cartridge, eluting with 5% to 20% methanolic ammonia in dichloromethane), triturated with acetonitrile, isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 65 °C to provide 169 mg of 1-{4-amino-2-(hydroxymethyl)-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as an off-white solid, mp 157 – 160 °C.

Anal. calcd for $C_{25}H_{28}N_6O_3 \cdot 0.5\ H_2O$: C, 63.95; H, 6.23; N, 17.90. Found: C, 63.59; H, 5.87; N, 17.97.

Example 76

1-{4-Amino-2-(hydroxymethyl)-7-[5-(hydroxymethyl)pyridin-3-yl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol



A suspension of 1-{4-amino-2-(ethoxymethyl)-7-[5-(hydroxymethyl)pyridin-3-yl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol (627 mg, 1.48 mmol), obtained from the filtrate from the trituration in Example 68, in dichloromethane (25 mL) was cooled to -78 °C. Boron tribromide (15 mL of a 1 M solution in dichloromethane) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for 3.5 hours. Methanol (50 mL) was carefully added, and the resulting solution was stirred at room temperature for 30 minutes and concentrated under reduced pressure. A solution of ammonia in methanol (50 mL of 1 M) was added, and the mixture was stirred for 30 minutes. Silica gel was added, and the mixture was concentrated under reduced pressure. The resulting mixture was purified by automated flash chromatography (FLASH 40+M cartridge, eluting with 15% to 30% methanolic ammonia in dichloromethane). All fractions containing product were combined and concentrated, and the residue was dissolved in methanol (50 mL) and treated with 6 M hydrochloric acid. The solution was heated at 50 °C for two hours, concentrated under reduced pressure, and diluted with 2 N ammonia in methanol. Silica gel was added, and the mixture was concentrated under reduced pressure. Chromatographic purification was carried out again as described above with the modification that the elution gradient began with 5% methanolic ammonia in dichloromethane. The resulting product was dissolved in methanol (20 mL), divided in ten equal portions, and loaded onto ten Waters Oasis Sample Extractions Cartridge MCX columns (500 mg) according to the following procedure. Each column was washed with methanol (2 volumes) and 1 N ammonia in methanol (3 volumes), and the ammonia washes were combined and concentrated under reduced pressure. The resulting solid (200 mg) was triturated with acetonitrile, isolated by

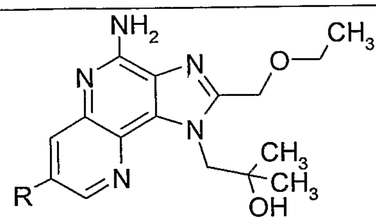
filtration, washed with acetonitrile, and dried in a vacuum oven to provide 175 mg of 1-{4-amino-2-(hydroxymethyl)-7-[5-(hydroxymethyl)pyridin-3-yl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl}-2-methylpropan-2-ol as a light yellow solid, mp 149-151 °C. Anal. calcd for $C_{20}H_{22}N_6O_3$: C, 60.90; H, 5.62; N, 21.31. Found: C, 60.75; H, 5.69; N, 21.40.

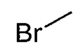
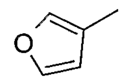
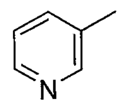
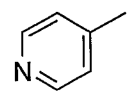
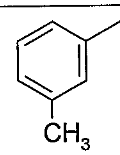
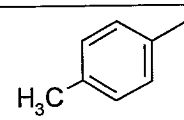
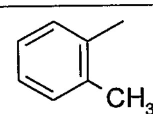
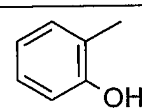
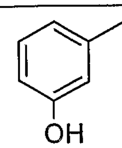
Examples 77 - 127

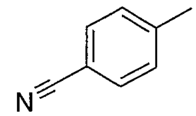
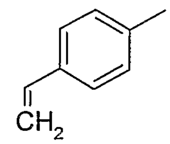
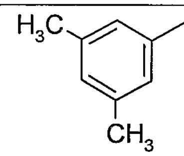
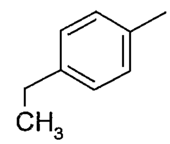
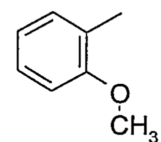
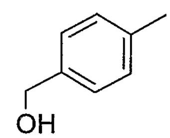
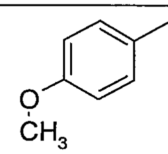
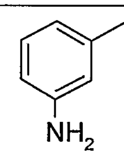
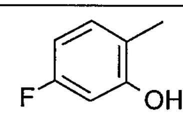
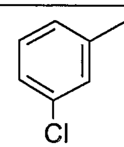
A solution of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (42.0 mg, 0.11 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.12 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. Palladium (II) acetate (0.150 mL of a 4 mg/mL solution in toluene, 0.0027 mmol), 2 M aqueous sodium carbonate solution (600 µL), deionized water (113 µL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53 µL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath.

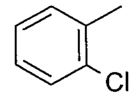
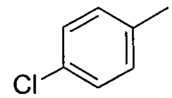
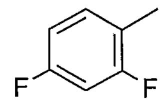
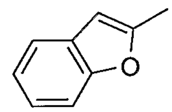
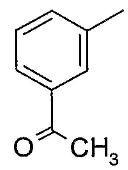
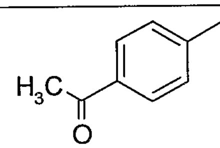
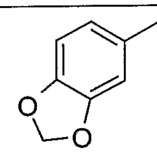
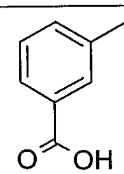
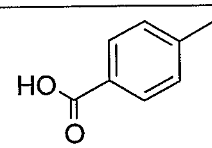
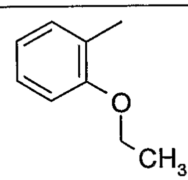
The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the procedure described in Examples 4 - 58. The resulting basic solutions were concentrated by vacuum centrifugation. The compounds were purified by reversed phase prep HPLC using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

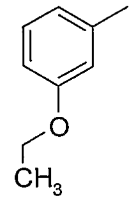
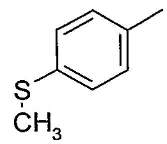
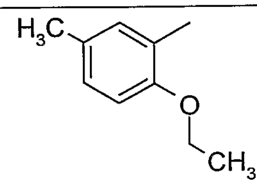
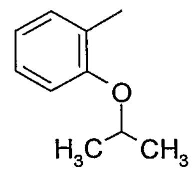
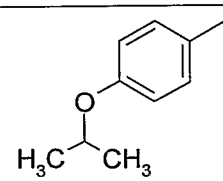
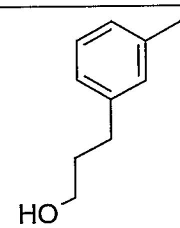
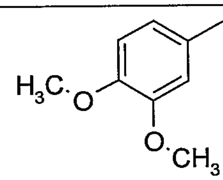
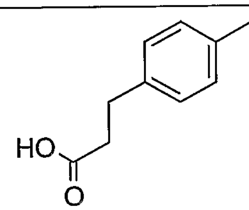
Examples 77 - 127

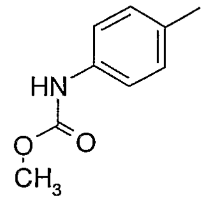
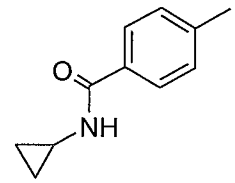
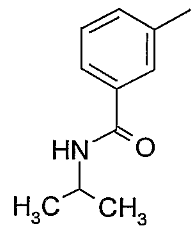
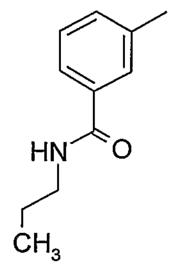
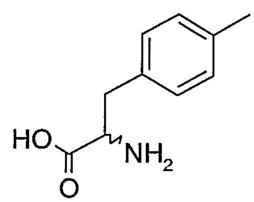
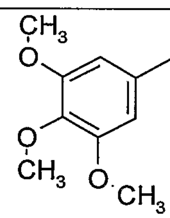
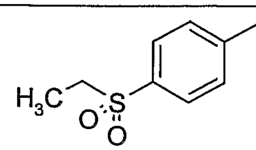


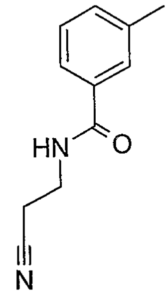
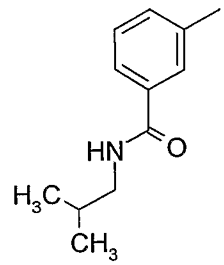
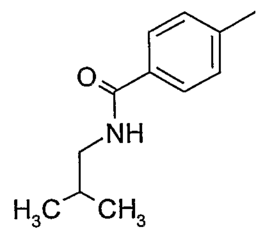
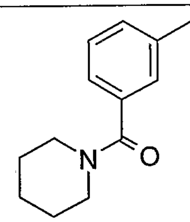
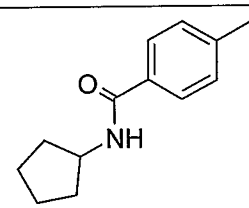
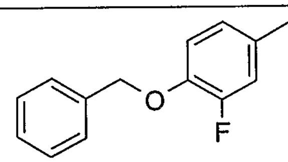
Example	Reagent	R	Measured Mass (M+H)
	None		394.0867
77	Furan-3-boronic acid		382.1894
78	Pyridine-3-boronic acid		393.2059
79	Pyridine-4-boronic acid		393.2078
80	3-Methylphenylboronic acid		406.2238
81	4-Methylphenylboronic acid		406.2264
82	*o*-Tolylboronic acid		406.2216
83	2-Hydroxyphenylboronic acid		408.2068
84	3-Hydroxyphenylboronic acid		408.2061

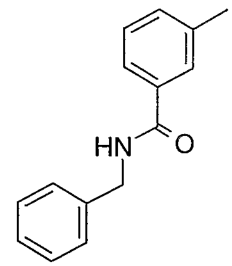
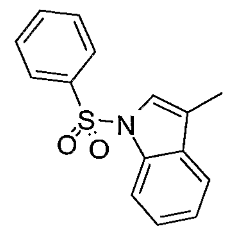
85	4-Cyanophenylboronic acid		417.2075
86	4-Vinylphenylboronic acid		418.2259
87	3,5-Dimethylphenylboronic acid		420.2406
88	4-Ethylphenylboronic acid		420.2379
89	2-Methoxyphenylboronic acid		422.2213
90	4-(Hydroxymethyl)phenylboronic acid		422.2196
91	4-Methoxyphenylboronic acid		422.2149
92	3-Aminophenylboronic acid monohydrate		407.2189
93	(4-Fluoro-2-hydroxy)phenylboronic acid		426.1971
94	3-Chlorophenylboronic acid		426.1695

95	2-Chlorophenylboronic acid		426.1694
96	4-Chlorophenylboronic acid		426.1713
97	2,4-Difluorophenylboronic acid		428.1916
98	Benzo[*b*]furan-2-boronic acid		432.2041
99	3-Acetylphenylboronic acid		434.2236
100	4-Acetylphenylboronic acid		434.2192
101	3,4-Methylenedioxyphenylboronic acid		436.1993
102	3-Carboxyphenylboronic acid		436.2005
103	4-Carboxyphenylboronic acid		436.1992
104	2-Ethoxyphenylboronic acid		436.2338

105	3-Ethoxyphenylboronic acid		436.2353
106	4-(Methylthio)phenylboronic acid		438.1939
107	2-Ethoxy-5-methylphenylboronic acid		450.2491
108	2-Isopropoxyphenylboronic acid		450.2470
109	4-Isopropoxyphenylboronic acid		450.2492
110	[3-(Hydroxypropyl)phenyl]boronic acid		450.2535
111	3,4-Dimethoxyphenylboronic acid		452.2313
112	3-(4-Boronophenyl)propionic acid		464.2318

113	4-(Methoxycarobonylamino)phenyl-boronic acid		465.2205
114	4-(Cyclopropylaminocarbonyl)phenyl-boronic acid		475.2462
115	3-(*N*-Isopropylaminocarbonyl)phenyl-boronic acid		477.2596
116	3-(*N*-Propylaminocarbonyl)phenyl-boronic acid		477.2637
117	4-Borono-*DL*-phenylalanine		479.2398
118	3,4,5-Trimethoxyphenylboronic acid		482.2416
119	4-(Ethylsulfonyl)phenylboronic acid		484.2023

120	3-(2-Cyanoethylaminocarbonyl)-phenylboronic acid		488.2415
121	3-(Isobutylaminocarbonyl)phenyl-boronic acid		491.2749
122	4-(Isobutylaminocarbonyl)phenyl-boronic acid		491.2750
123	3-(Piperidine-1-carbonyl)phenylboronic acid		503.2775
124	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		503.2757
125	4-Benzyloxy-3-fluorophenylboronic acid		516.2405

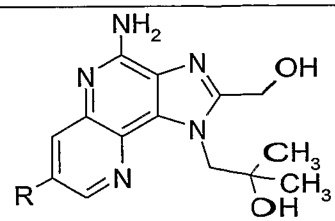
126	3-(*N*-Benzylaminocarbonyl)phenyl-boronic acid		525.2625
127	1-(Phenylsulfonyl)-1*H*-indol-3-ylboronic acid		571.2138

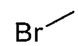
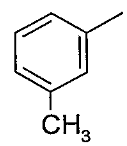
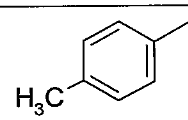
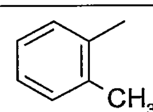
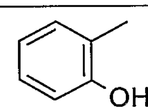
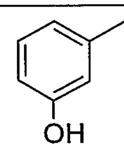
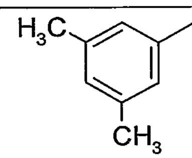
Examples 128 – 151

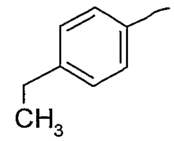
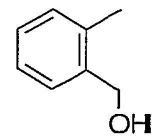
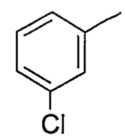
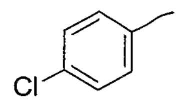
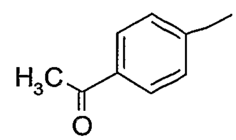
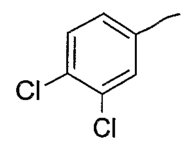
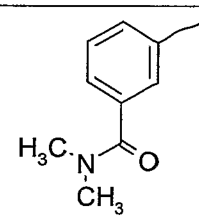
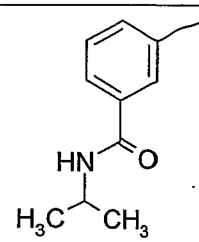
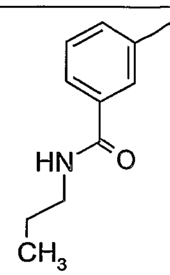
A solution of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (53.0 mg, 0.135 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.16 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. Palladium (II) acetate (0.198 mL of a 4 mg/mL solution in toluene, 0.0035 mmol), 2 M aqueous sodium carbonate solution (813 µL), deionized water (113 µL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (70 µL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. Each sample was purified using Waters Oasis Sample Extractions Cartridge MCX according to the method described in Examples 4 – 58, and the resulting basic solution was concentrated by vacuum centrifugation. The residue from each tube was dissolved in dichloromethane (1 mL) with the aid of sonication. Each tube was placed in an ice bath for five minutes to cool to 0 °C, and then boron tribromide (0.640 mL of a 1 M solution in dichloromethane) was added. The solution was vortexed, stirred at 0 °C for 30 minutes, and then stirred overnight at room temperature. Methanol (1 mL) and 6 N hydrochloric acid (0.500 mL) were added to each tube. The contents were vortexed, and the volatiles were removed by vacuum centrifugation. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The table below

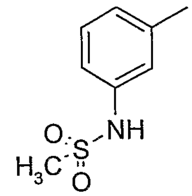
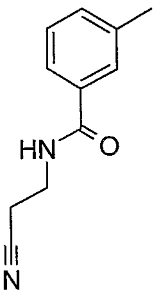
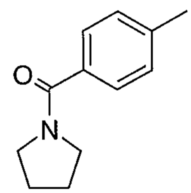
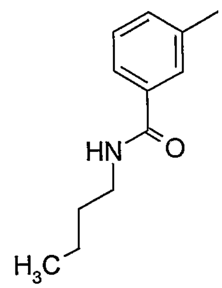
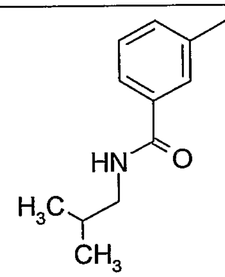
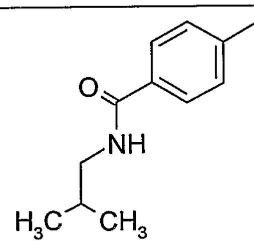
shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

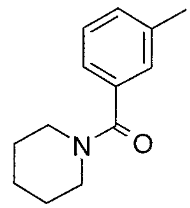
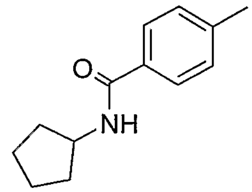
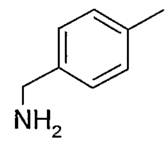
Examples 128 - 151



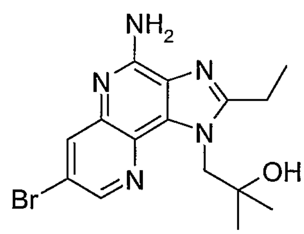
Example	Reagent	R	Measured Mass (M+H)
	None		366.0562
128	3-Methylphenylboronic acid		378.1936
129	4-Methylphenylboronic acid		378.1937
130	*o*-Tolylboronic acid		378.1938
131	2-Hydroxyphenylboronic acid		380.1721
132	3-Hydroxyphenylboronic acid		380.1718
133	3,5-Dimethylphenylboronic acid		392.2099

134	4-Ethylphenylboronic acid		392.2090
135	(2-Hydroxymethylphenyl)boronic acid dehydrate		394.1907
136	3-Chlorophenylboronic acid		398.1390
137	4-Chlorophenylboronic acid		398.1394
138	4-Acetylphenylboronic acid		406.1883
139	3,4-Dichlorophenylboronic acid		432.1010
140	3-(*N,N*-Dimethylaminocarbonyl)phenyl-boronic acid		435.2148
141	3-(*N*-Isopropylaminocarbonyl)phenyl-boronic acid		449.2317
142	3-(*N*-Propylaminocarbonyl)phenyl-boronic acid		449.2323

143	3-(Methylsulfonylamino)phenyl-boronic acid		457.1663
144	3-(2-Cyanoethylaminocarbonyl)-phenylboronic acid		460.2130
145	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		461.2330
146	3-(Butylaminocarbonyl)phenylboronic acid		463.2459
147	3-(Isobutylaminocarbonyl)phenyl-boronic acid		463.2463
148	4-(Isobutylaminocarbonyl)phenyl-boronic acid		463.2461

149	3-(Piperidine-1-carbonyl)phenylboronic acid		475.2453
150	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		475.2463
151	(4-Aminomethylphenyl)boronic acid, pinacol ester, hydrochloride		393.2034

Preparation of 1-(4-Amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol



Part A

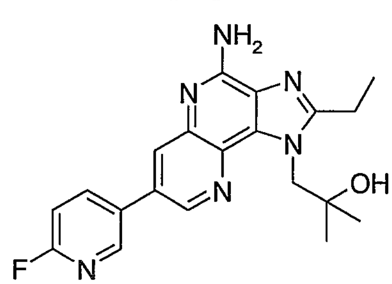
Pyridine hydrochloride (0.095 g, 0.82 mmol) and triethyl orthopropionate (6.36 g, 36.1 mmol) were sequentially added to a solution of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (10.2 g, 32.8 mmol) in toluene (200 mL), and the resulting mixture was heated at reflux for three hours. Most of the solvent was removed under reduced pressure, and a solid was present. The solid was isolated by filtration and dried to provide 8.59 g of 1-(7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as a light yellow solid. A small portion of the solid was recrystallized from acetonitrile to provide an off-white solid, mp 207-208 °C. Anal. calcd for $C_{15}H_{17}BrN_4O$: C, 51.59; H, 4.91; N, 16.04. Found: C, 51.27; H, 4.62; N, 15.78.

Part B

mCPBA (11.2 g of 75% purity, 48.7 mmol) was added to a stirred solution of 1-(7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (8.5 g, 24 mmol) in dichloromethane (150 mL), and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (100 mL), washed sequentially with 4% aqueous sodium carbonate (2 x 150 mL) and brine (1 x 150 mL), and concentrated under reduced pressure. The residue was dissolved in dichloromethane (150 mL), and concentrated ammonium hydroxide (80 mL) was added. The mixture was stirred vigorously and cooled to 4 °C, and then *p*-toluenesulfonyl chloride (5.80 g, 30.4 mmol) was added in portions. The reaction mixture was stirred at room temperature for 16 hours and diluted with dichloromethane (200 mL). A solid was present and was isolated by filtration, washed well with water and acetonitrile, and dried to provide 2.94 of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol. The organic layer was separated and washed with 4 N aqueous sodium carbonate (2 x 150 mL). The combined washings were extracted with dichloromethane (100 mL), and the combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with acetonitrile to provide an additional 1.36 g of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as an off-white solid, mp 235-236 °C. Anal. calcd for $C_{15}H_{18}BrN_5O$: C, 49.46; H, 4.98; N, 19.23. Found: C, 49.19; H, 4.84; N, 19.21.

Example 152

1-[4-Amino-2-ethyl-7-(6-fluoropyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol



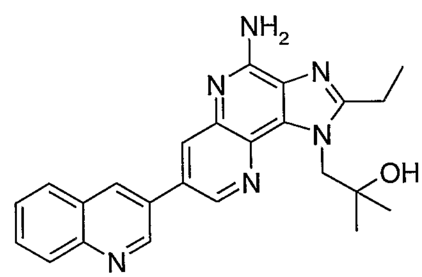
2-Fluoropyridine-5-boronic acid (0.468 g, 3.32 mmol) was added to 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (1.1 g, 3.0

mmol) and 1-propanol (10 mL). The mixture was degassed and backfilled with nitrogen. Triphenylphosphine (23.8 mg, 0.0900 mmol), aqueous sodium carbonate (4.53 mL of 2 M), and water (2 mL) were added followed by palladium (II) acetate (6.8 mg, 0.030 mmol). The yellow suspension was heated at reflux for two hours. Water (20 mL) was added, and the 1-propanol was removed under reduced pressure. The remaining mixture was extracted with chloroform (2 x 100 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was triturated with acetonitrile and isolated by filtration to provide 0.84 g of 1-[4-amino-2-ethyl-7-(6-fluoropyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as a white powder, mp 250-251 °C.

Anal. calcd for $C_{20}H_{21}FN_6O$: C, 63.15; H, 5.56; N, 22.09. Found: C, 63.03; H, 5.83; N, 22.13.

Example 153

1-[4-Amino-2-ethyl-7-(quinolin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol



The method described in Example 152 was used to treat 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (1.0 g, 2.7 mmol) and 3-quinolineboronic acid (0.52 g, 3.0 mmol) in 1-propanol (10 mL) with triphenylphosphine (21.6 mg, 0.0820 mmol), aqueous sodium carbonate (4.1 mL of 2 M), water (2 mL), and palladium (II) acetate (6.2 mg, 0.027 mmol) with the following modifications. The reaction mixture was heated at reflux for four hours. The crude product was purified by recrystallization from ethyl acetate to provide 0.58 g of 1-[4-amino-2-ethyl-7-(quinolin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as beige needles, mp > 270 °C.

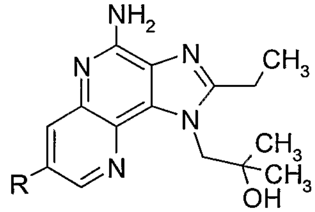
Anal. Calcd for $C_{24}H_{24}N_6O \cdot 0.3HCl$: C, 68.08; H, 5.78; N, 19.85. Found: C, 67.74; H, 5.63; N, 19.79.

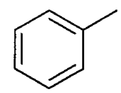
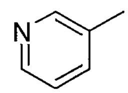
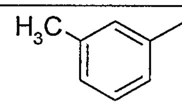
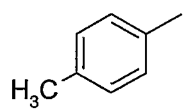
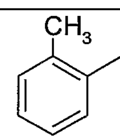
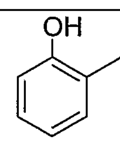
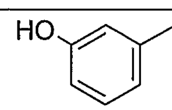
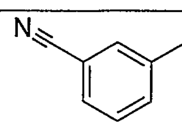
Examples 154 – 194

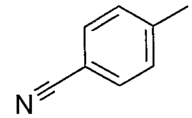
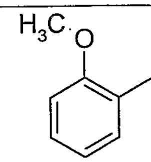
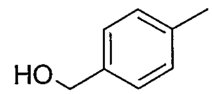
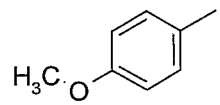
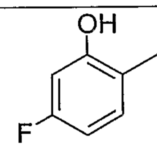
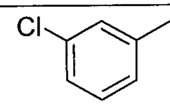
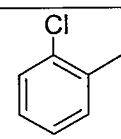
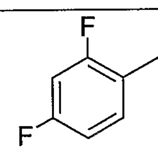
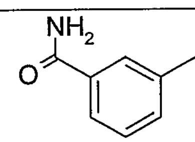
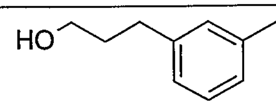
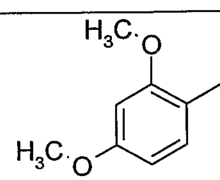
A solution of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (36.4 mg, 0.10 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (0.150 mL of a 4 mg/mL solution in toluene, 0.0027 mmol), 2 M aqueous sodium carbonate solution (600 μL), deionized water (113 μL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53 μL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. Methanol (1 mL) was added to each reaction, which was heated at 80 °C for six hours.

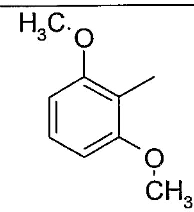
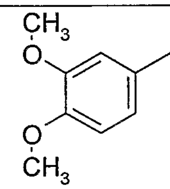
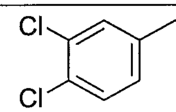
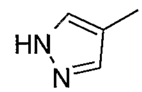
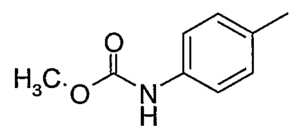
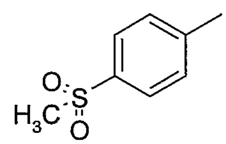
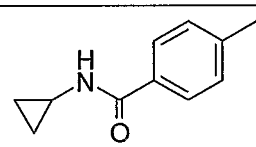
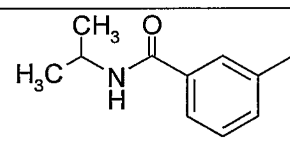
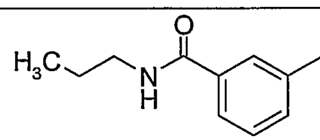
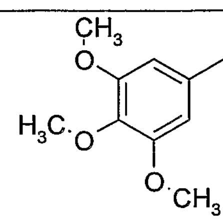
The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the procedure described in Examples 4 - 58. The resulting basic solutions were concentrated by vacuum centrifugation. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

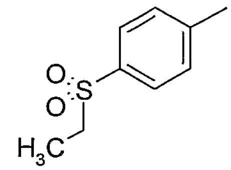
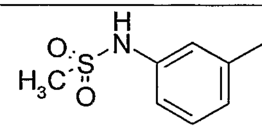
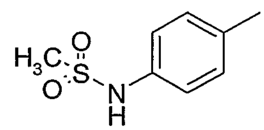
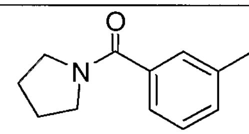
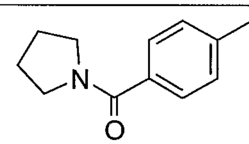
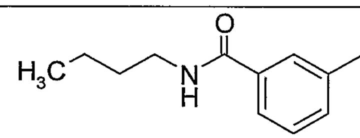
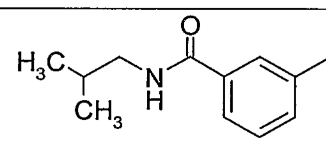
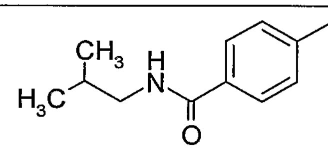
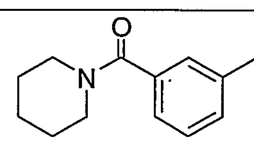
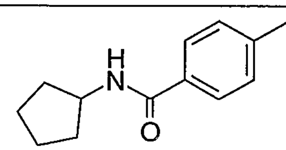
Examples 154 - 194

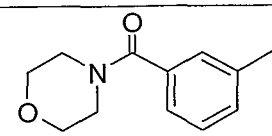
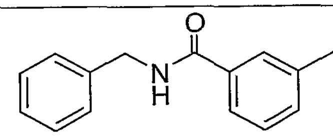


Example	Reagent	R	Measured Mass (M+H)
	None	Br	364.0771
154	Phenylboronic acid		362.1984
155	Pyridine-3-boronic acid		363.1940
156	3-Methylphenylboronic acid		376.2139
157	4-Methylphenylboronic acid		376.2125
158	*o*-Tolylboronic acid		376.2099
159	2-Hydroxyphenylboronic acid		378.1943
160	3-Hydroxyphenylboronic acid		378.1950
161	3-Cyanophenylboronic acid		387.1916

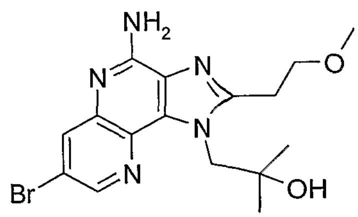
162	4-Cyanophenylboronic acid		387.1917
163	2-Methoxyphenylboronic acid		392.2068
164	4-(Hydroxymethyl)phenylboronic acid		392.2070
165	4-Methoxyphenylboronic acid		392.2078
166	(4-Fluoro-2-hydroxy)phenylboronic acid		396.1834
167	3-Chlorophenylboronic acid		396.1577
168	2-Chlorophenylboronic acid		396.1611
169	2,4-Difluorophenylboronic acid		398.1794
170	(3-Aminocarbonylphenyl)-boronic acid		405.2054
171	[3-(Hydroxypropyl)phenyl]-boronic acid		420.2407
172	2,4-Dimethoxyphenylboronic acid		422.2228

173	2,6-Dimethoxyphenylboronic acid		422.2192
174	3,4-Dimethoxyphenylboronic acid		422.2192
175	3,4-Dichlorophenylboronic acid		430.1209
176	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl-1*H*-pyrazole		352.1907
177	4-(Methoxycarobonylamino)-phenylboronic acid		435.2133
178	4-(Methanesulfonyl)phenyl-boronic acid		440.1761
179	4-(Cyclopropylaminocarbonyl)-phenylboronic acid		445.2351
180	3-(*N*-Isopropylaminocarbonyl)-phenylboronic acid		447.2488
181	3-(*N*-Propylaminocarbonyl)-phenylboronic acid		447.2490
182	3,4,5-Trimethoxyphenylboronic acid		452.2300

183	4-(Ethylsulfonyl)phenylboronic acid		454.1888
184	3-(Methylsulfonylamino)-phenylboronic acid		455.1872
185	4-(Methylsulfonylamino)-phenylboronic acid		455.1880
186	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		459.2503
187	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		459.2505
188	3-(Butylaminocarbonyl)-phenylboronic acid		461.2662
189	3-(Isobutylaminocarbonyl)-phenylboronic acid		461.2663
190	4-(Isobutylaminocarbonyl)-phenylboronic acid		461.2668
191	3-(Piperidine-1-carbonyl)phenylboronic acid		473.2675
192	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		473.2658

193	3-(Morpholine-4-carbonyl)phenylboronic acid		475.2444
194	3-(*N*-Benzylaminocarbonyl)-phenylboronic acid		495.2519

Preparation of 1-[4-Amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol



Part A

Triethylamine (35.95 mL, 257.9 mmol) was added to a suspension of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (49.6 g, 172 mmol) in dichloromethane (500 mL). 1-Amino-2-methylpropan-2-ol (16.86 g, 189 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 hours and then concentrated under reduced pressure. The residue was triturated with water and stirred for 1 hour. The precipitated solid was isolated by filtration, washed with water, and dried. This material was suspended in diethyl ether (400 mL), sonicated, isolated by filtration, and then dried in a vacuum oven at 40 °C for 16 hours to provide 58.1 g of 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow solid, mp 189-190 °C.

Part B

A Parr vessel was charged with 5% platinum on carbon (5.8 g) and a suspension of 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (58.00 g) in acetonitrile (800 mL) and methanol (400 mL). The vessel was placed under hydrogen pressure (30 psi, 2.1 X 10^5 Pa) for 8 hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filtrate was concentrated under reduced pressure to provide 52.70 g of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow solid.

Part C

3-Methoxypropionyl chloride (24.90 g, 203 mmol) was added over a period of five minutes to a mixture of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (52.70 g, 169 mmol), chloroform (100 mL), and acetonitrile (530 mL). The reaction mixture was stirred at room temperature overnight. The precipitated solid was isolated by filtration, washed well with acetonitrile, and then dried to provide 60.10 g of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-3-methoxypropionamide hydrochloride as a brown solid, mp 206-208 °C.

Part D

A mixture of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-3-methoxypropionamide hydrochloride (60.00 g, 138 mmol), potassium carbonate (60 g), water (300 mL), and ethanol (900 mL) was heated at reflux for 16 hours and then concentrated under reduced pressure. The precipitated solid was isolated by filtration, washed sequentially with water and methanol, and dried to provide a brown solid. This material was dissolved in a 3/1 mixture of chloroform/methanol and decolorized with activated charcoal to provide 38.5 g of 1-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a white solid, mp 125 °C. Anal. calcd for $C_{16}H_{19}BrN_4O_2$: %C, 50.67; %H, 5.05; %N, 14.77; Found: %C, 50.86; %H 4.94; %N, 15.01.

Part E

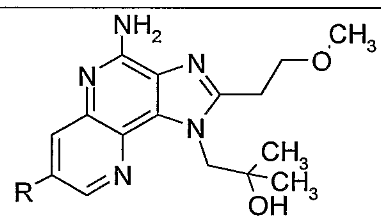
mCPBA (34.77 g of 75% pure material, 151 mmol) was added to a solution of 1-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (38.2 g, 101 mmol) in dichloromethane (450 mL) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with dichloromethane (200 mL), washed sequentially with 4% aqueous sodium carbonate (2 x 150 mL) and brine (1 x 150 mL), and concentrated under reduced pressure to provide the *N*-oxide derivative. The *N*-oxide derivative was combined with dichloromethane (450 mL) and concentrated ammonium hydroxide (200 mL) and the mixture was cooled in an ice bath. *p*-Toluenesulfonyl chloride (24 g) was added in portions. After the addition was complete the ice bath was removed and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with dichloromethane (200 mL). Suspended solids were isolated by filtration, washed with water, and dried to provide 7.60 g of 1-[4-amino-7-

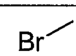
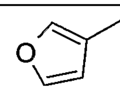
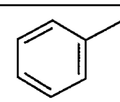
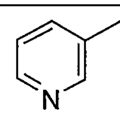
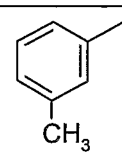
bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as an off white solid, mp 210-211 °C.

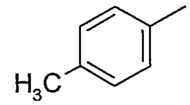
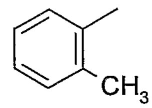
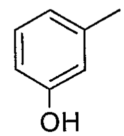
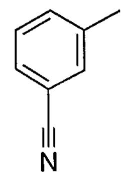
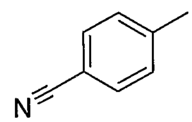
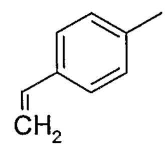
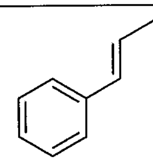
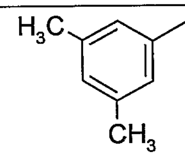
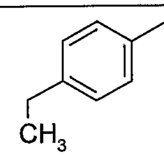
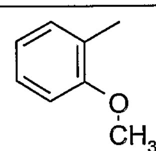
Anal. Calcd for $C_{16}H_{20}BrN_5O_2$: C, 48.74; H, 5.11; N, 17.76. Found: C, 48.63; H, 5.10; N, 17.80.

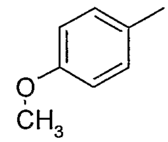
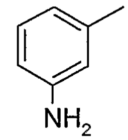
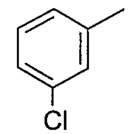
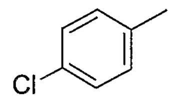
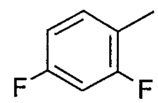
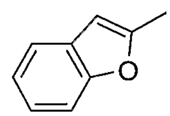
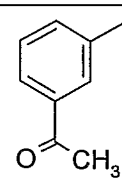
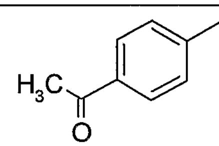
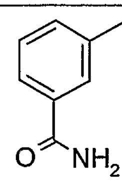
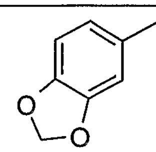
Examples 195 - 239

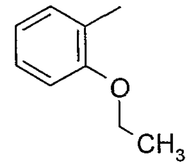
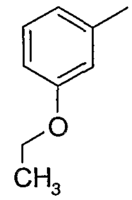
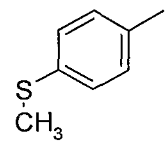
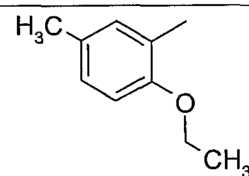
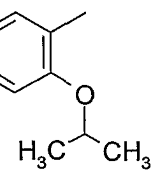
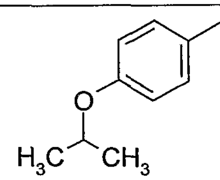
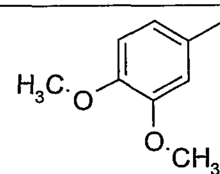
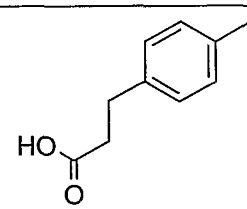
The methods described in Examples 154 – 194 were followed using 1-[4–amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (39.6 mg, 0.100 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol with the modification that the samples were not diluted in methanol after the initial heating at 80 °C overnight. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

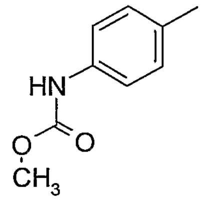
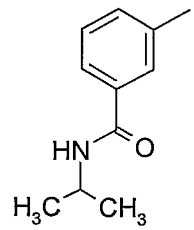
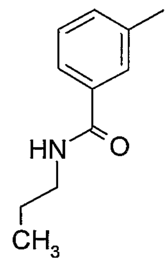
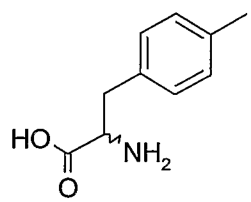
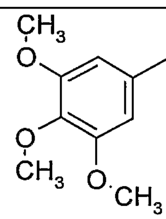
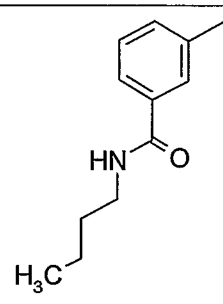


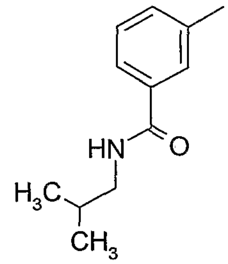
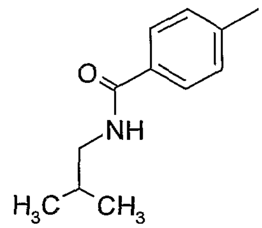
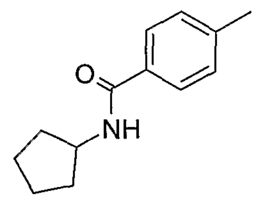
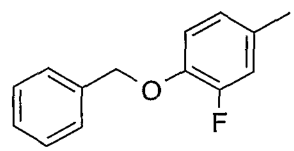
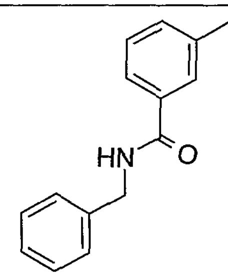
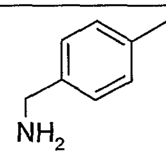
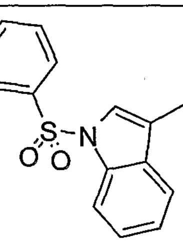
Example	Reagent	R	Measured Mass (M+H)
	None		394.0905
195	Furan-3-boronic acid		382.1880
196	Phenylboronic acid		392.2085
197	Pyridine-3-boronic acid		393.2048
198	3-Methylphenylboronic acid		406.2235

199	4-Methylphenylboronic acid		406.2226
200	*o*-Tolylboronic acid		406.2256
201	3-Hydroxyphenylboronic acid		408.2012
202	3-Cyanophenylboronic acid		417.2042
203	4-Cyanophenylboronic acid		417.2022
204	4-Vinylphenylboronic acid		418.2255
205	*E*-Phenylethenylboronic acid		418.2242
206	3,5-Dimethylphenylboronic acid		420.2391
207	4-Ethylphenylboronic acid		420.2406
208	2-Methoxyphenylboronic acid		422.2182

209	4-Methoxyphenylboronic acid		422.2198
210	3-Aminophenylboronic acid monohydrate		407.2192
211	3-Chlorophenylboronic acid		426.1703
212	4-Chlorophenylboronic acid		426.1657
213	2,4-Difluorophenylboronic acid		428.1884
214	Benzo[*b*]furan-2-boronic acid		432.2018
215	3-Acetylphenylboronic acid		434.2191
216	4-Acetylphenylboronic acid		434.2188
217	(3-Aminocarbonylphenyl)-boronic acid		435.2119
218	3,4-Methylenedioxyphenylboronic acid		436.1964

219	2-Ethoxyphenylboronic acid		436.2356
220	3-Ethoxyphenylboronic acid		436.2342
221	4-(Methylthio)phenylboronic acid		438.1961
222	2-Ethoxy-5-methylphenylboronic acid		450.2529
223	2-Isopropoxyphenylboronic acid		450.2491
224	4-Isopropoxyphenylboronic acid		450.2483
225	3,4-Dimethoxyphenylboronic acid		452.2301
226	3-(4-Boronophenyl)propionic acid		464.2289

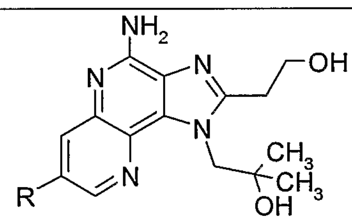
227	4-(Methoxycarobonylamino)phenyl boronic acid		465.2238
228	3-(*N*-Isopropylaminocarbonyl)-phenylboronic acid		477.2588
229	3-(*N*-Propylaminocarbonyl)-phenylboronic acid		477.2597
230	4-Borono-*DL*-phenylalanine		479.2408
231	3,4,5-Trimethoxyphenylboronic acid		482.2391
232	3-(Butylaminocarbonyl)phenyl-boronic acid		491.2756

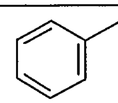
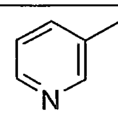
233	3-(Isobutylaminocarbonyl)-phenylboronic acid		491.2758
234	4-(Isobutylaminocarbonyl)-phenylboronic acid		491.2774
235	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		503.2751
236	4-Benzyloxy-3-fluorophenylboronic acid		516.2403
237	3-(*N*-Benzylaminocarbonyl)-phenylboronic acid		525.2590
238	(4-Aminomethylphenyl)boronic acid Pinacol Ester, hydrochloride		421.2362
239	1-(Phenylsulfonyl)-1*H*-indol-3-ylboronic acid		571.2127

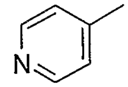
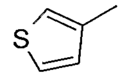
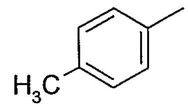
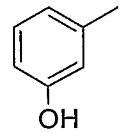
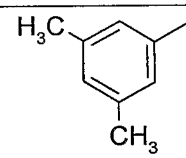
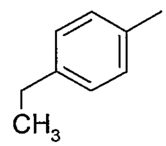
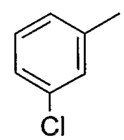
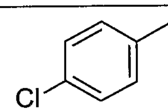
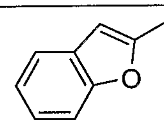
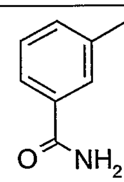
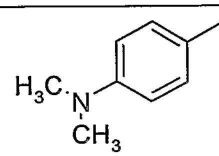
Examples 240 - 272

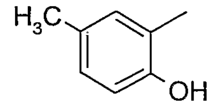
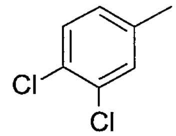
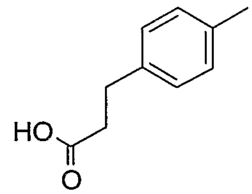
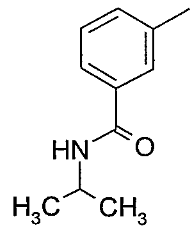
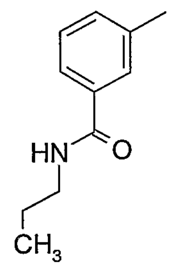
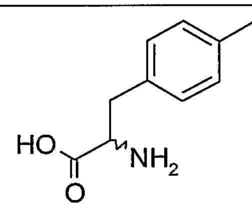
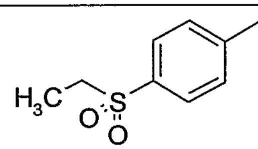
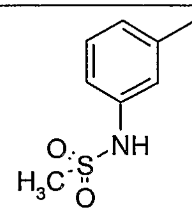
The methods described in Examples 154 – 194 were followed using 1-[4-amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (39.5 mg, 0.100 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol. After the samples were heated overnight, Example 241 was driven to completion by adding additional palladium (II) acetate (0.150 mL), heating for 30 minutes at 80 °C, adding pyridine-3-boronic acid (0.11 mmol) and methanol (1 mL), and heating at 80 °C for 16 hours. After each sample was purified using Waters Oasis Sample Extractions Cartridge MCX according to the method described in Examples 4 – 58, and the resulting basic solution was concentrated by vacuum centrifugation, the reaction with boron tribromide described in Examples 128 – 151 was carried out using 0.400 mL of boron tribromide solution for each test tube. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

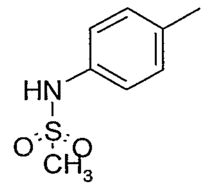
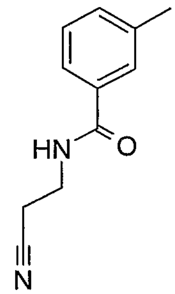
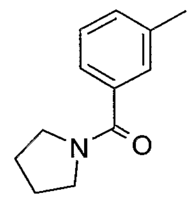
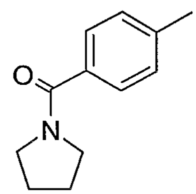
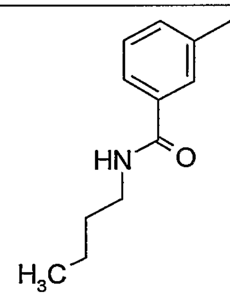
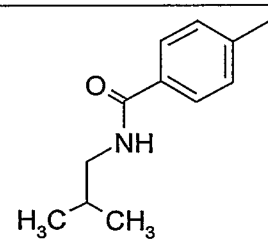
Examples 240 - 272

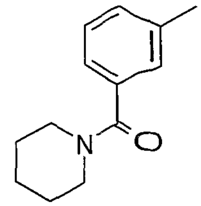
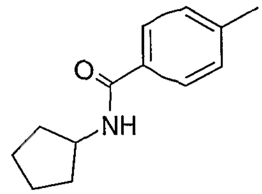
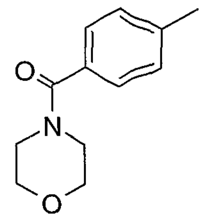
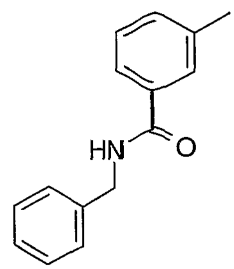
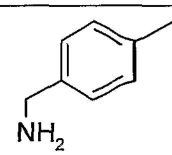
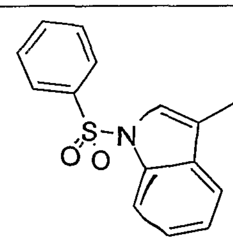


Example	Reagent	R	Measured Mass (M+H)
240	Phenylboronic acid		378.1948
241	Pyridine-3-boronic acid		379.1908

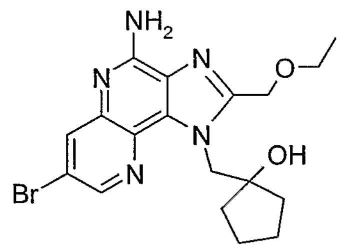
242	Pyridine-4-boronic acid		379.1918
243	Thiophene-3-boronic acid		384.1483
244	4-Methylphenylboronic acid		392.2052
245	3-Hydroxyphenylboronic acid		394.1910
246	3,5-Dimethylphenylboronic acid		406.2278
247	4-Ethylphenylboronic acid		406.2274
248	3-Chlorophenylboronic acid		412.1532
249	4-Chlorophenylboronic acid		412.1524
250	Benzo[*b*]furan-2-boronic acid		418.1891
251	(3-Aminocarbonylphenyl)-boronic acid		421.1974
252	4-(*N*,*N*-Dimethylamino)phenyl-boronic acid		421.2391

253	2-Ethoxy-5-methylphenylboronic acid		408.2050
254	3,4-Dichlorophenylboronic acid		446.1184
255	3-(4-Boronophenyl)propionic acid		450.2180
256	3-(*N*-Isopropylaminocarbonyl)-phenylboronic acid		463.2501
257	3-(*N*-Propylaminocarbonyl)-phenylboronic acid		463.2482
258	4-Borono-*DL*-phenylalanine		465.2278
259	4-(Ethylsulfonyl)phenylboronic acid		470.1879
260	3-(Methylsulfonylamino)-phenylboronic acid		471.1835

261	4-(Methylsulfonylamino)-phenylboronic acid		471.1864
262	3-(2-Cyanoethylaminocarbonyl) phenylboronic acid		474.2297
263	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		475.2468
264	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		475.2480
265	3-(Butylaminocarbonyl)-phenylboronic acid		477.2648
266	4-(Isobutylaminocarbonyl)-phenylboronic acid		477.2640

267	3-(Piperidine-1-carbonyl)phenylboronic acid		489.2656
268	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		489.2626
269	4-(Morpholine-4-carbonyl)phenylboronic acid		491.2423
270	3-(*N*-Benzylaminocarbonyl)-phenylboronic acid		511.2478
271	(4-Aminomethylphenyl)boronic acid pinacol ester, hydrochloride		407.2218
272	1-(Phenylsulfonyl)-1*H*-indol-3-ylboronic acid		557.2020

Preparation of 1-{[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol



Part A

To a solution of cyclopentanone (40.0 mL, 452 mmol) in nitromethane (36 mL) and ethanol (14 mL) was added a solution of sodium ethoxide in ethanol (2.67 M, 8.5 mL, 23 mmol). The solution was stirred for five days at room temperature. Water (400 mL) was added, and the mixture was extracted with ethyl acetate (2 x 350 mL). The combined organic extracts were washed with water (2 x 200 mL) and brine (200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The starting materials and solvent were removed from the product by distillation under reduced pressure to yield 8.3 g of 1-(nitromethyl)cyclopentanol as a yellow liquid.

Part B

A mixture of 1-(nitromethyl)cyclopentanol (8.3 g, 57 mmol) and 20% palladium hydroxide on carbon (0.6 g) in ethanol (150 mL) was hydrogenated at 35 psi (2.4×10^5 Pa) on a Parr apparatus for one day. After workup, the reaction was not complete and was subjected to the reaction conditions again for eight days using fresh catalyst. The mixture was filtered through CELITE filter agent and the filtrate was concentrated to yield an oil that contained a 13:1 ratio of the desired amine product, 1-(aminomethyl)cyclopentanol, to the corresponding hydroxylamine. The oil was concentrated from toluene. Material from a separate run was used in the next step.

Part C

A suspension of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (54.42 g, 188.6 mmol) in chloroform (820 mL) was cooled to 0 °C, and triethylamine (105 mL, 755 mmol) was added. A solution of 1-(aminomethyl)cyclopentanol (28.25 g, 245.2 mmol) in chloroform (272 mL) was added slowly over a period of 15 minutes. The reaction was allowed to warm to room temperature and stirred for 30 minutes. The solution was washed sequentially with water (500 mL) and saturated aqueous sodium bicarbonate (750

mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1-{[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]methyl}cyclopentanol.

Part D

The material from Part C was dissolved in acetonitrile (1.66 L) and isopropyl alcohol (496 mL) and added to a Parr vessel. Catalytic 5% platinum on carbon (6.6 g) was added, and the reaction mixture was placed under hydrogen pressure for three days and filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure to provide 1-{[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]methyl}cyclopentanol.

Part E

Ethoxyacetyl chloride (25.4 g, 207 mmol) was added to a mixture of the material from Part D and acetonitrile (1.27 L). The reaction was stirred at room temperature, and over the course of two hours, additional ethoxyacetyl chloride (20.8 g, 0.170 mol) was added. The solvent was removed under reduced pressure to provide *N*-(7-bromo-4-{[(1-hydroxycyclopentyl)methyl]amino}[1,5]naphthyridin-3-yl)-2-ethoxyacetamide hydrochloride.

Part F

Triethylamine (38 mL, 270 mmol) was added to a suspension of the material from Part E in ethanol (380 mL), and the resulting solution was heated at reflux (85 °C) for seven hours, allowed to cool to room temperature, and stirred overnight. The volatiles were removed under reduced pressure, and the residue was partitioned between chloroform (800 mL) and water (200 mL). The organic layer was separated, washed with brine (2 x 300 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide 1-{[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol as a brown solid.

Part G

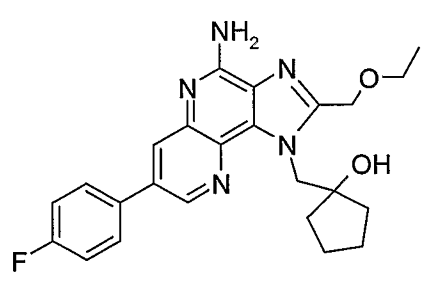
mCBPA (21 g of about 50% pure material, 61 mmol) was added to a solution of 1-{[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol (18.89 g, 46.6 mmol) in chloroform (190 mL), and the reaction was stirred for one hour at room temperature. Additional mCPBA (11 g) was added, and the reaction was stirred for an additional 30 minutes. Concentrated ammonium hydroxide (40 mL) was added slowly followed by *p*-toluenesulfonyl chloride (9.32 g, 48.9 mmol).

The reaction was stirred for one hour at room temperature, and additional chloroform (600 mL) was added. The reaction was stirred for one additional hour, and additional *p*-toluenesulfonyl chloride (4.45 g, 23.3 mmol) and ammonium hydroxide (10 mL) were added. After the reaction mixture was stirred for an additional 1.5 hours, it was filtered to remove a precipitate. The filtrate layers were separated, and the organic phase was washed with saturated aqueous sodium bicarbonate (2 x 200 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue (25.86 g) was triturated with acetonitrile at 98 °C, and a solid impurity was removed by filtration. The acetonitrile was removed under reduced pressure, and the residue was dissolved in chloroform. The resulting solution was washed with 1% aqueous sodium carbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 98.5:1.5 chloroform:methanol) and then triturated with acetonitrile at 98 °C, isolated by filtration at room temperature, and dried in a vacuum oven at 110 °C over two nights to provide 4.83 g of 1-{[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol as a white solid, mp 166-167.5 °C.

Anal. calcd for $C_{18}H_{22}BrN_5O_2$: C, 51.44; H, 5.28; N, 16.66. Found: C, 51.32; H, 5.24; N, 16.63.

Example 273

1-{[4-Amino-2-(ethoxymethyl)-7-(4-fluorophenyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol



1-{[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol (1.13 g, 2.7 mmol), 4-fluorobenzeneboronic acid (0.43 g, 3.1 mmol), triphenylphosphine (6.3 mg, 0.024 mmol), and 5:1 (v/v) 1-propanol/water (6.6 mL) were combined under a nitrogen atmosphere. A 5 mg/mL solution of palladium (II) acetate (1.8 mg, 0.008 mmol) in toluene and aqueous sodium carbonate (1.8 mL of 2 M)

were sequentially added. The reaction mixture was heated at reflux for two hours, allowed to cool to room temperature, and partitioned between chloroform (75 mL) and brine (20 mL). The organic fraction was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue (1.27 g) was purified by trituration with acetonitrile at 98 °C followed by recrystallization from chloroform/hexane. The crystals were dried in a vacuum oven at 110 °C for two hours to provide 0.67 g of 1-{[4-amino-2-(ethoxymethyl)-7-(4-fluorophenyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol as a steel-gray solid, mp 212-212.5°C.

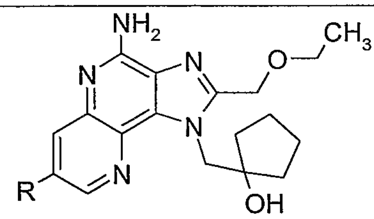
MS (APCI) *m/z* 436 $(M + H)^+$;

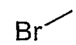
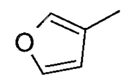
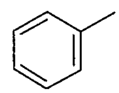
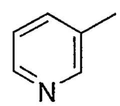
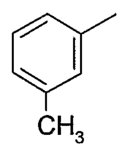
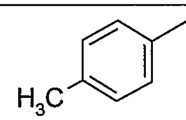
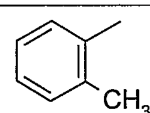
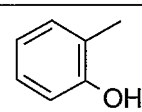
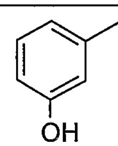
Anal. calcd for $C_{24}H_{26}FN_5O_2$: C, 66.19; H, 6.02; N, 16.08. Found: C, 66.16; H, 5.82; N, 16.09.

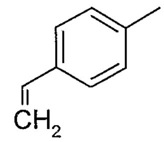
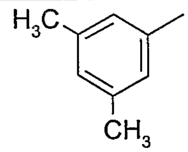
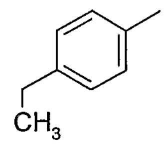
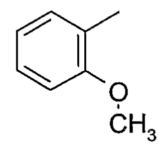
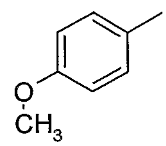
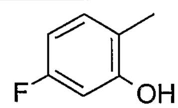
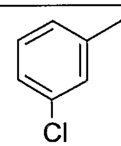
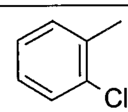
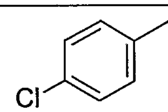
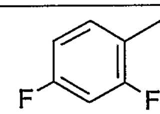
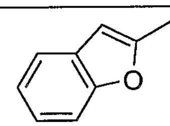
Examples 274 - 318

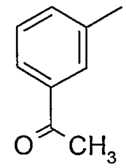
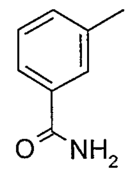
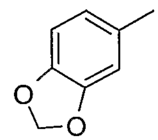
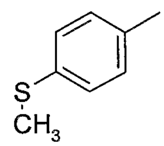
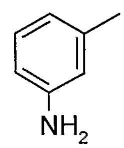
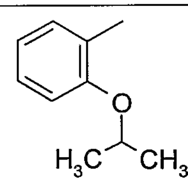
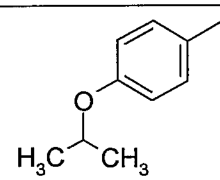
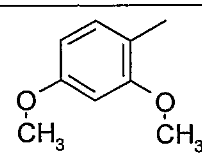
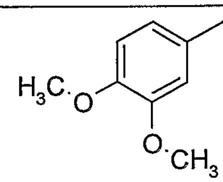
The methods described in Examples 154 – 194 were followed using 1-{[4-amino-2-(ethoxymethyl)-7-(4-fluorophenyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol (42 mg, 0.10 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol with the modification that the samples were not diluted in methanol after the initial heating at 80 °C overnight. After Example 318 was heated, it was treated with glacial acetic acid (0.500 mL) in deionized water (0.500 mL) and tetrahydrofuran (THF) (0.500 mL) and heated at 60 °C for four hours before the purification procedures. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

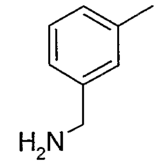
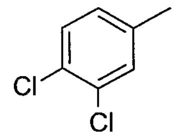
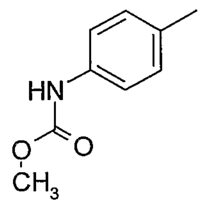
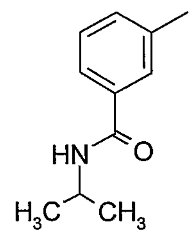
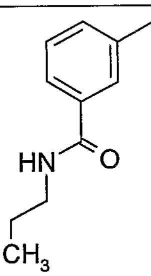
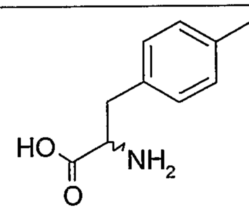
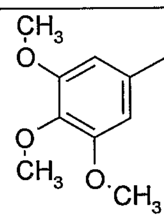
Examples 274 - 318

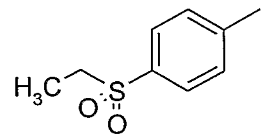
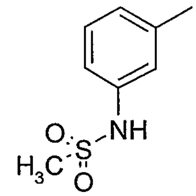
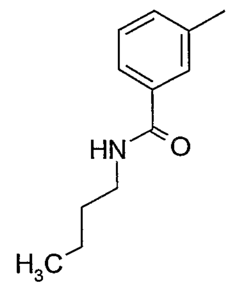
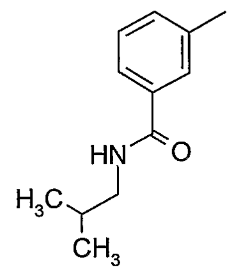
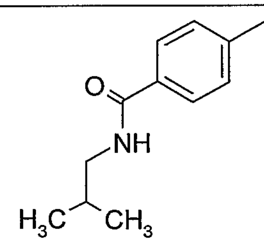
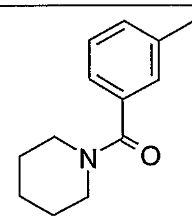
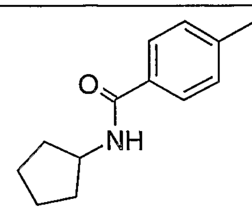


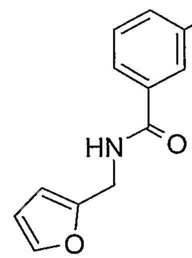
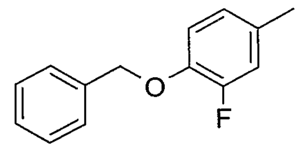
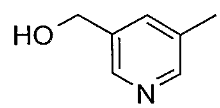
Example	Reagent	R	Measured Mass (M+H)
	None		420.1010
274	Furan-3-boronic acid		408.2018
275	Phenylboronic acid		418.2246
276	Pyridine-3-boronic acid		419.2180
277	3-Methylphenylboronic acid		432.2399
278	4-Methylphenylboronic acid		432.2399
279	*o*-Tolylboronic acid		432.2370
280	2-Hydroxyphenylboronic acid		434.2184
281	3-Hydroxyphenylboronic acid		434.2200

282	4-Vinylphenylboronic acid		444.2399
283	3,5-Dimethylphenylboronic acid		446.2534
284	4-Ethylphenylboronic acid		446.2546
285	2-Methoxyphenylboronic acid		448.2359
286	4-Methoxyphenylboronic acid		448.2319
287	(4-Fluoro-2-hydroxy)phenylboronic acid		452.2119
288	3-Chlorophenylboronic acid		452.1844
289	2-Chlorophenylboronic acid		452.1846
290	4-Chlorophenylboronic acid		452.1821
291	2,4-Difluorophenylboronic acid		454.2068
292	Benzo[*b*]furan-2-boronic acid		458.2165

293	3-Acetylphenylboronic acid		460.2357
294	(3-Aminocarbonylphenyl)-boronic acid		461.2298
295	3,4-Methylenedioxyphenyl-boronic acid		462.2112
296	4-(Methylthio)phenylboronic acid		464.2138
297	3-Aminophenylboronic acid monohydrate		433.2337
298	2-Isopropoxyphenylboronic acid		476.2664
299	4-Isopropoxyphenylboronic acid		476.2672
300	2,4-Dimethoxyphenyl-boronic acid		478.2456
301	3,4-Dimethoxyphenylboronic acid		478.2443

302	(3-Aminomethylphenyl)-boronic acid, hydrochloride		447.2491
303	3,4-Dichlorophenylboronic acid		486.1453
304	4-(Methoxycarbonylamino)-phenylboronic acid		491.2386
305	3-(*N*-Isopropylaminocarbonyl)-phenylboronic acid		503.2766
306	3-(*N*-Propylaminocarbonyl)phenyl boronic acid		503.2786
307	4-Borono-*DL*-phenylalanine		505.2545
308	3,4,5-Trimethoxyphenylboronic acid		508.2562

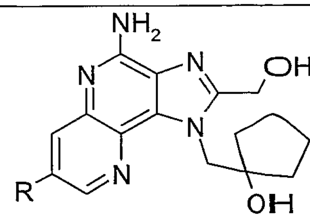
309	4-(Ethylsulfonyl)phenylboronic acid		510.2166
310	3-(Methylsulfonylamino)phenyl boronic acid		511.2104
311	3-(Butylaminocarbonyl)-phenylboronic acid		517.2953
312	3-(Isobutylaminocarbonyl)-phenylboronic acid		517.2916
313	4-(Isobutylaminocarbonyl)-phenylboronic acid		517.2930
314	3-(Piperidine-1-carbonyl)phenylboronic acid		529.2957
315	4-(Cyclopentylaminocarbonyl)-phenylboronic acid		529.2908

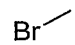
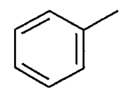
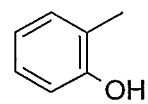
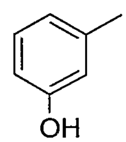
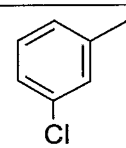
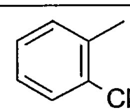
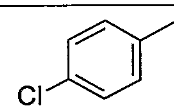
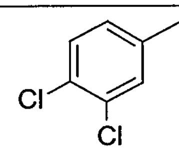
316	3-(Furfurylaminocarbonyl)phenylboronic acid		541.2592
317	4-Benzyloxy-3-fluorophenylboronic acid		542.2554
318	5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		449.2278

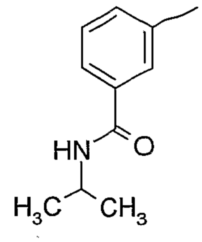
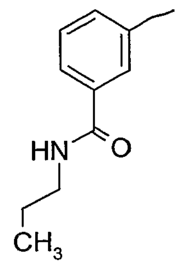
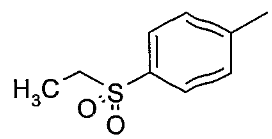
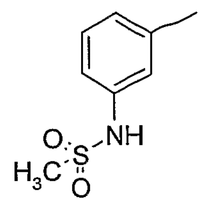
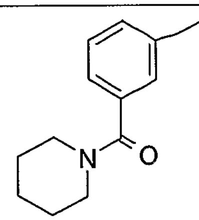
Examples 319 - 330

The methods described in Examples 154 – 194 were followed using 1-{[4-amino-2-(ethoxymethyl)-7-(4-fluorophenyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]methyl}cyclopentanol (42 mg, 0.10 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol with the modification that the samples were not diluted in methanol after the initial heating at 80 °C overnight. After each sample was purified using Waters Oasis Sample Extractions Cartridge MCX according to the method described in Examples 4 – 58, and the resulting basic solution was concentrated by vacuum centrifugation, the reaction with boron tribromide described in Examples 128 – 151 was carried out using 0.400 mL of boron tribromide solution for each test tube. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

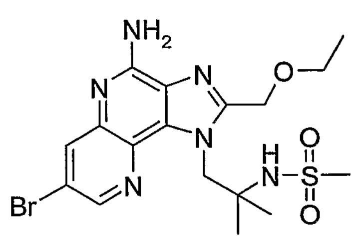
Example 319 - 330



Example	Reagent	R	Measured Mass (M+H)
	None		392.0712
319	Phenylboronic acid		390.1926
320	2-Hydroxyphenylboronic acid		406.1866
321	3-Hydroxyphenylboronic acid		406.1866
322	3-Chlorophenylboronic acid		424.1538
323	2-Chlorophenylboronic acid		424.1515
324	4-Chlorophenylboronic acid		424.1515
325	3,4-Dichlorophenylboronic acid		458.1111

326	3-(*N*-Isopropylaminocarbonyl)-phenylboronic acid		475.2462
327	3-(*N*-Propylaminocarbonyl)-phenylboronic acid		475.2446
328	4-(Ethylsulfonyl)phenylboronic acid		482.1849
329	3-(Methylsulfonylamino)-phenylboronic acid		483.1805
330	3-(Piperidine-1-carbonyl)phenylboronic acid		501.2579

Preparation of *N*-{2-[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}methanesulfonamide



Part A

A modification of the method described in Part A of the preparation of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-

ol was followed using 150 g (0.42 mol) of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine and 1,2-diamino-2-methylpropane (80.7 g, 0.915 mol) in lieu of 1-amino-2-methylpropan-2-ol. The reaction was at 3 °C at the start of the addition of the diamine. Following the addition, the reaction was stirred for 4.5 hours before it was concentrated under reduced pressure. *N*-1-(7-Bromo-3-nitro[1,5]naphthyridin-4-yl)-2-methylpropane-1,2-diamine (140 g) was obtained after drying over two nights in a vacuum oven at 35 °C.

Part B

A solution of sodium hydroxide (11.8 g,) in deionized water (295 mL) was added dropwise to a solution of *N*-1-(7-bromo-3-nitro[1,5]naphthyridin-4-yl)-2-methylpropane-1,2-diamine (100.0 g, 294.0 mmol) in tetrahydrofuran (1.3 L). A solution of di-*tert*-butyl dicarbonate (72.8 g, 333 mmol) in THF (219 mL) was added slowly over a period of 25 minutes. The reaction was stirred at room temperature for three days. The THF was removed under reduced pressure, and the resulting mixture was diluted with deionized water (1 L) and extracted twice with dichloromethane (1.5 L). The combined extracts were washed sequentially with saturated aqueous sodium carbonate (2 x 900 mL) and brine (250 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 141 g of *tert*-butyl 2-[(7-bromo-3-nitro[1,5]naphthyrdin-4-yl)amino]-1,1-dimethylethylcarbamate.

Part C

A modification of the method described in Part B of the preparation of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol was used to reduce *tert*-butyl 2-[(7-bromo-3-nitro[1,5]naphthyrdin-4-yl)amino]-1,1-dimethylethylcarbamate (138.0 g, 313.4 mmol). The reaction was placed under hydrogen pressure for 5.5 hours. The reaction yielded 128 g of *tert*-butyl 2-[(3-amino-7-bromo[1,5]naphthyrdin-4-yl)amino]-1,1-dimethylethylcarbamate containing some acetonitrile.

Part D

The method described in Part C of the preparation of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol was used to treat *tert*-butyl 2-[(3-amino-7-bromo[1,5]naphthyrdin-4-yl)amino]-1,1-dimethylethylcarbamate (64.0 g, 0.156 mol) with ethoxyacetyl chloride (21.0 g, 0.171 mol) in acetonitrile (640 mL). At the completion of the reaction, additional acetonitrile

(200 mL) was added, and the solid product was isolated by filtration, washed with a small volume of acetonitrile, and dried for four hours to provide 55.6 g of *tert*-butyl 2-({7-bromo-3-[(ethoxyacetyl)amino][1,5]naphthyrdin-4-yl}amino)-1,1-dimethylethylcarbamate hydrochloride.

Part E

A modification of the method described in Part D of the preparation of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol was used to treat *tert*-butyl 2-({7-bromo-3-[(ethoxyacetyl)amino][1,5]naphthyrdin-4-yl}amino)-1,1-dimethylethylcarbamate (55.6 g, 0.104 mol) with potassium carbonate (55.6 g). After the ethanol was removed under reduced pressure, and the resulting mixture was extracted with dichloromethane (4 x 300 mL). The combined extracts were concentrated under reduced pressure to provide 51 g of *tert*-butyl {2-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}carbamate as a yellowish brown solid.

Part F

A modification of the method described in Part B of the preparation of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol was used to treat the material from Part E above with mCPBA (37.52 g of 75%, 163.1 mmol) in dichloromethane (800 mL) followed by ammonium hydroxide (200 mL) and *p*-toluenesulfonyl chloride (25.90 g, 135.9 mmol) in dichloromethane (450 mL). After the reaction was complete and diluted with dichloromethane (200 mL), it was washed with 4N aqueous sodium carbonate (2 x 200 mL). The combined aqueous fractions were washed extracted with dichloromethane (200 mL), and the combined organic fractions were washed with brine, dried over sodium sulfated, filtered, and concentrated under reduced pressure. The residue was triturated with acetonitrile to provide 18.77 g of *tert*-butyl {2-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}carbamate as an off-white solid. A portion was recrystallized from acetonitrile to provide the following analytical data, mp 176-178 °C.

Anal. calcd for $C_{21}H_{29}BrN_6O_3$: C, 51.12; H, 5.92; N, 17.03. Found: C, 51.07; H, 5.92; N, 17.09.

Part G

Hydrogen chloride (56.74 g of a 2.2 M solution in ethanol, 124.8 mmol) was added to a suspension of *tert*-butyl {2-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}carbamate (15.40 g, 31.21 mmol) in anhydrous ethanol (120 mL), and the reaction mixture was heated at reflux for four hours and allowed to cool to room temperature. A precipitate had formed and was isolated by filtration, washed with a small volume of cold ethanol, and dried in a vacuum oven at 60 °C to provide 12.26 g of 1-(2-amino-2-methylpropyl)-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine dihydrochloride.

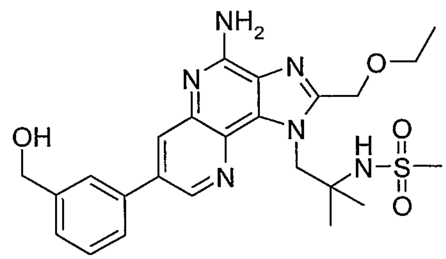
Part H

Triethylamine (13.02 g, 128.7 mmol) was added to a suspension of 1-(2-amino-2-methylpropyl)-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine dihydrochloride (6.00 g, 12.9 mmol) in dichloromethane (500 mL), and the reaction was cooled to 4 °C. A solution of methanesulfonyl chloride (1.62 g, 14.2 mmol) in dichloromethane (10 mL) was then added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 24 hours, diluted with dichloromethane (200 mL), washed sequentially with water (200 mL), 4% aqueous sodium carbonate (2 x 200 mL), water (200 mL), and brine (200 mL), and concentrated under reduced pressure. The crude product was purified by automated flash chromatography (FLASH 40+M silica cartridge, eluting with 0 to 25% CMA in chloroform) followed by recrystallization from acetonitrile to provide 5.21 g of *N*-{2-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}methanesulfonamide as a white solid, 211-212 °C.

Anal. calcd for $C_{17}H_{23}BrN_6O_3S$: C, 43.32; H, 4.92; N, 17.83. Found: C, 43.35; H, 4.85; N, 18.07.

Example 331

N-(2-{4-Amino-2-(ethoxymethyl)-7-[3-(hydroxymethyl)phenyl]-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl}-1,1-dimethylethyl)methanesulfonamide



The method described in Example 152 was used to treat N-{2-[4-amino-7-bromo-2-(ethoxymethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}methanesulfonamide (1.2 g, 2.55 mmol) and 3-(hydroxymethyl)benzeneboronic acid (0.58 g, 3.8 mmol) in 1-propanol (15 mL) with triphenylphosphine (20.0 mg, 0.0760 mmol), aqueous sodium carbonate (3.82 mL of 2 M), water (3 mL), and palladium (II) acetate (5.7 mg, 0.025 mmol) with the following modifications. The reaction mixture was heated at reflux overnight. The crude product was purified by automated flash chromatography (FLASH 40+M cartridge, eluting with 0% to 35% CMA in chloroform) followed by recrystallization from acetonitrile to provide 0.98 g of N-(2-{4-amino-2-(ethoxymethyl)-7-[3-(hydroxymethyl)phenyl]-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl}-1,1-dimethylethyl)methanesulfonamide as a white solid, mp 173-174 °C.

MS (APCI) m/z 499.33 $(M + H)^+$;

Anal. Calcd for $C_{24}H_{30}N_6O_4S$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.67; H, 5.80; N, 16.90.

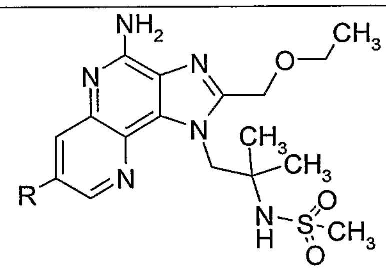
Examples 332 - 336

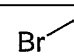
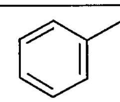
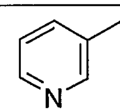
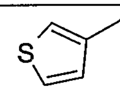
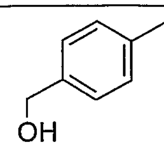
N-{2-[4-Amino-7-bromo-2-(ethoxymethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl]-1,1-dimethylethyl}methanesulfonamide (0.100 g, 0.21 mmol) was added to a test tube. The boronic acid (0.22 mmol) indicated in the table below and n-propanol (3.2 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (0.300 mL of a 4 mg/mL solution in toluene, 0.0053 mmol), 2M aqueous sodium carbonate solution (1.2 mL), deionized water (226 µL), and a solution of 0.15 mol% triphenylphosphine in n-propanol (106 µL, 0.016 mmol) were sequentially added. The

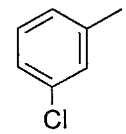
test tube was purged with nitrogen, capped, and then heated at 80 °C for four hours in a sand bath.

The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the procedure described in Examples 4 - 58. The resulting basic solutions were concentrated by vacuum centrifugation. Half of the material from each tube was purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The other half of the material was used in Examples 337 – 338. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Example 332 - 336



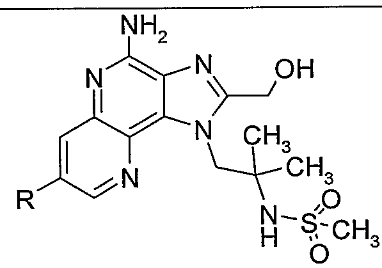
Example	Reagent	R	Measured Mass (M+H)
	None		471.0826
332	Phenylboronic acid		469.2024
333	Pyridine-3-boronic acid		470.1975
334	Thiophene-3-boronic acid		475.1560
335	4-(Hydroxymethyl)-phenylboronic acid		499.2130

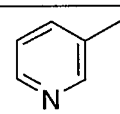
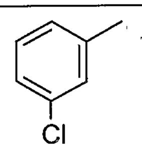
336	3-Chlorophenylboronic acid		503.1670

Example 337 - 338

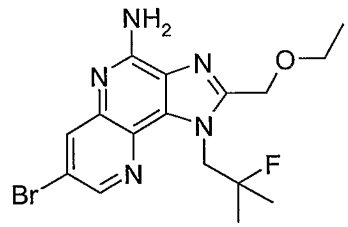
The reserved material from Examples 332 – 336 was subjected to the reaction with boron tribromide described in Examples 128 – 151 using 0.400 mL of boron tribromide solution for each test tube. After each reaction was stirred for four hours at room temperature, additional boron tribromide (0.200 mL of 1 M in dichloromethane) was added. The reaction was stirred for one hour at room temperature and allowed to stand for 65 hours. Methanol (1 mL) and 6 N hydrochloric acid (0.500 mL) were added to each tube. The contents were vortexed for 30 minutes, and the volatiles were removed by vacuum centrifugation. The compounds were purified by reversed phase prep HPLC according to the method described in Examples 77 – 127. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 337 – 338



Example	Reagent	R	Measured Mass (M+H)
337	Pyridine-3-boronic acid		442.1650
338	3-Chlorophenylboronic acid		475.1310

Preparation of 7-Bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

A solution of *tert*-butyl 2-hydroxy-2-methylpropylcarbamate (19.2 g, 101 mmol) in dichloromethane (500 mL) was stirred at –78 °C under a nitrogen atmosphere, and (diethylamino)sulfur trifluoride (DAST) (18.0 g, 112 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. Saturated aqueous sodium bicarbonate (150 mL) was added. The organic layer was then separated and washed sequentially with saturated aqueous sodium bicarbonate (150 mL), water (150 mL), and brine (150 mL); dried over magnesium sulfate; filtered; and concentrated under reduced pressure. The resulting oil was purified by automated flash chromatography (FLASH 65I cartridge, eluting with 10% ethyl acetate in hexane) to provide 13.7 g of *tert*-butyl 2-fluoro-2-methylpropylcarbamate as a light yellow oil that crystallized overnight.

Part B

Hydrogen chloride (50 mL of a 4 M solution in 1,4-dioxane) was added to a solution of *tert*-butyl 2-fluoro-2-methylpropylcarbamate (13.7 g, 71.6 mmol) in dichloromethane (300 mL), and the reaction was stirred for five hours at room temperature and concentrated under reduced pressure. The residue was three times dissolved in toluene and concentrated under reduced pressure to provide 8.08 g of 2-fluoro-2-methylpropan-1-amine hydrochloride as a white solid.

Part C

Triethylamine (17.3 g, 171 mmol) was added to a suspension of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (52.2 mmol) in DMF (50 mL), and then a solution of 2-fluoro-2-methylpropan-1-amine hydrochloride (5.46 g, 42.8 mmol) in DMF (25 mL) was added dropwise over a period of ten minutes. The reaction mixture was stirred at room temperature for 14.5 hours, and water (500 mL) was added. The resulting mixture was stirred for one hour. A solid was present and was isolated by filtration, washed with

water, and dried overnight in a vacuum oven at 65 °C to provide 14.7 g of 7-bromo-*N*-(2-fluoro-2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a reddish-brown solid.

Part D

A Parr vessel was charged with 5% platinum on carbon (700 mg), 7-bromo-*N*-(2-fluoro-2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (7.00 g, 20.4 mmol), and acetonitrile (50 mL) and placed under hydrogen pressure (30 psi, 2.1 X 10^5 Pa) for two hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 6.22 g of 7-bromo-*N*-(2-fluoro-2-methylpropyl)[1,5]naphthyridin-3,4-diamine as a dark brown oil.

Part E

Ethoxyacetyl chloride (2.7 g, 22 mmol) was added dropwise to a solution of 7-bromo-*N*-(2-fluoro-2-methylpropyl)[1,5]naphthyridin-3,4-diamine (6.2 g, 19.8 mmol) in acetonitrile (65 mL). The reaction was stirred for 20 minutes at room temperature and concentrated under reduced pressure. The residue was treated with potassium carbonate (4.1 g, 29.7 mmol) in ethanol (90 mL) and water (30 mL) according to the method described in Part D of the preparation of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol with the modification that the reaction was stirred at room temperature for 19 hours and then heated at reflux for five hours. After the drying step 6.65 g of product were obtained. A portion of the isolated product (0.5 g) was purified by automated flash chromatography (40+M silica cartridge, eluting with 3% to 10% methanol in dichloromethane) followed by recrystallization from acetonitrile. The crystals were isolated by filtration, washed with cold acetonitrile, and dried in a vacuum oven at 65 °C to provide 21 mg of analytically pure 7-bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as white needles, mp 127-128 °C.

Anal. Calcd for $C_{16}H_{18}BrFN_4O$: C, 50.41; H, 4.76; N, 14.70. Found: C, 50.42; H, 4.73; N, 14.78.

Part F

mCPBA (5.4 g of 77% purity, 24 mmol) was added to a stirred solution of 7-bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (6.1 g, 16 mmol) in chloroform (160 mL), and the reaction was

stirred at room temperature for 17.5 hours. Concentrated ammonium hydroxide (80 mL) was added, and then *p*-toluenesulfonyl chloride (3.7 g, 19.2 mmol) was added over a period of five minutes. The reaction mixture was stirred at room temperature for 1.5 hours, and an analysis by LC/MS indicated the presence of starting material. Additional *p*-toluenesulfonyl chloride (3.7 g) was added, and the reaction mixture was stirred at room temperature for three hours. The aqueous layer was separated and extracted with dichloromethane (3 x 100 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue (14.5 g) was triturated with dichloromethane (50 mL), isolated by filtration, and washed with dichloromethane to provide 970 mg of desired product. The filtrate was concentrated under reduced pressure, and the residue was triturated with methanol, isolated by filtration, washed with methanol, and dried in a vacuum oven at 65 °C for five hours to provide an additional 2.45 g of product. Silica gel was added to the filtrate. The mixture was concentrated under reduced pressure and purified by automated flash chromatography (FLASH 65I cartridge, eluting with 3% to 10% methanol in ethyl acetate) to provide 530 mg of product. A portion of the isolated material (220 mg) was recrystallized from acetonitrile (50 mL). The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 80 °C to provide 92 mg of analytically pure 7-bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid, mp 221-222 °C.

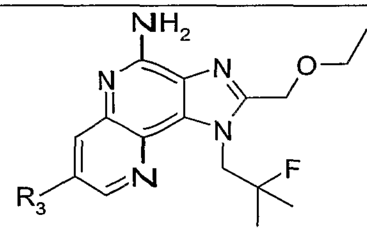
Anal. Calcd for $C_{16}H_{19}BrFN_5O$: C, 48.50; H, 4.83; N, 17.67. Found: C, 48.60; H, 4.69; N, 17.64.

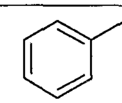
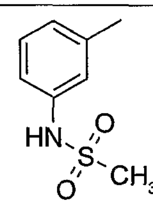
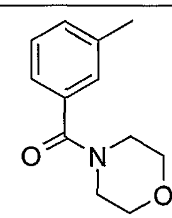
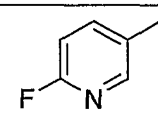
Examples 339 – 342

Under a nitrogen atmosphere, a suspension of 7-bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.600 g, 1.51 mmol), the boronic acid indicated in the following table (1.82 mmol), potassium carbonate (0.691 g, 5.00 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.011 g, 0.015 mmol), DME (7 mL), and water (3 mL) was stirred in a pressure vessel. The vessel was sealed, and the suspension was heated at 110 °C for the time indicated in the following table, allowed to cool to room temperature, and concentrated under reduced pressure. The residue was dissolved in methanol and dichloromethane. Silica gel was added, and the

mixture was concentrated under reduced pressure. The residue was purified by automated flash chromatography (FLASH 40+M cartridge, eluting with methanol in ethyl acetate with the percentage of methanol given in the table). Acetonitrile was added to the purified product to form a solid, which was isolated by filtration, washed with acetonitrile, and dried in a vacuum oven at 65 °C or 80 °C to provide the products with the structures indicated in the table. Analytical data is provided below the table.

Examples 339 - 342



Example	Boronic acid	Reaction Time	Methanol in eluent	R_3
339	Phenylboronic acid	64 hours	3% to 10%	
340	(3-Methylsulfonylamino-phenyl)boronic acid	14.5 hours	3% to 12%	
341	3-(Morpholine-4-carbonyl)-phenylboronic acid	16 hours	5% to 15%	
342	6-Fluoropyridine-3-boronic acid	16 hours	3% to 10%	

Example 339: 2-(Ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (150 mg) was obtained as a white solid, mp 173-174 °C. Anal. Calcd for $C_{22}H_{24}FN_5O$: C, 67.16; H, 6.15; N, 17.80. Found: C, 67.09; H, 6.31; N, 17.71.

Example 340: *N*-{3-[4-Amino-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]phenyl}methanesulfonamide (126 mg) was obtained as a white solid, mp 208-209 °C.

Anal. Calcd for $C_{23}H_{27}FN_6O_3S$: C, 56.78; H, 5.59; N, 17.27. Found: C, 56.67; H, 5.41; N, 17.23.

Example 341: 2-(Ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-7-[3-(morpholin-4-ylcarbonyl)phenyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin–4-amine (192 mg) was obtained as a white solid, mp 167-168 °C.

Anal. Calcd for $C_{27}H_{31}FN_6O_3$: C, 64.02; H, 6.17; N, 16.59. Found: C, 63.80; H, 6.01; N, 16.67.

Example 342: 2-(Ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-7-(6-fluoropyridin-3-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (177 mg) was obtained as a white solid, mp 198-199 °C.

Anal. Calcd for $C_{21}H_{22}F_2N_6O$: C, 61.16; H, 5.38; N, 20.38. Found: C, 60.95; H, 5.17; N, 20.48.

Examples 343 – 350

The methods described in Examples 154 – 194 were followed using 7-bromo-2-(ethoxymethyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (40.0 mg, 0.100 mmol) instead of 1-(4-amino-7-bromo-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol with the modification that the samples were not diluted in methanol after the initial heating at 80 °C overnight. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.